



UNIVERSITY *of* LIMERICK

O L L S C O I L L U I M N I G H

**Development of a Falls Risk Prediction Tool for
Use with People with Multiple Sclerosis**

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**A thesis submitted in fulfilment of the requirements for the degree of Doctor of
Philosophy at the University of Limerick.**

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‘Development of a Falls Risk Prediction Tool for Use with People with Multiple Sclerosis’ Gillian Quinn

Abstract:

People with Multiple Sclerosis (MS) present with a wide range of symptoms including sensory, motor and visual impairment as well as cognitive dysfunction and fatigue. Many of these symptoms affect mobility and balance and have been shown to be associated with falls risk among this population. It is known that falls are prevalent among people with MS, with a high rate of multiple falls and injurious falls. While much is known about the factors and serious consequences associated with falls, as of yet there is no reliable stand-alone clinical measure or multivariable model suitable to assess falls risk in a busy clinic setting. Thus, the aim of this thesis was to develop a simple falls risk screening model suitable for use in everyday clinical practice.

To understand what clinical measures of balance are currently useful in identifying falls risk in MS, a systematic review and meta-analysis was carried out. There was significant heterogeneity across the included studies and discriminative ability of the measures is commonly not reported. The Timed Up and Go (TUG) did show significant difference between fallers and non-fallers in retrospective study designs, is commonly used and does not require specialist equipment, and thus was investigated in a prospective cohort that monitored falls using diaries for 3 months.

The association between dual task cost and falls was explored in more depth by examining objectively measured dual task cost and subjective problems dual tasking. Different patterns of cognitive -motor interference and their association to faller status was also analysed. Results showed that objectively measured dual task cost is not associated with an increased falls risk but self-report problems of difficulty doing two things at once doubled the risk of falling with an associated risk ratio of 2.07 (CI 1.15-3.71).

From the main longitudinal study multiple clinical and objective variables were analysed to determine the model with the greatest sensitivity and best discriminative ability for identifying falls risk in people with MS. Following multivariable regression analysis, the model with the greatest sensitivity (88%) and predictive validity (AUC = 0.72, 95% CI 0.62-0.82), included the variables of history of a fall, no visual problems, problems with bladder control and a slower speed on the TUG.

The clinical implications arising from this research are important; firstly, all healthcare professionals working with people with MS should ask about history of falls, visual problems, problems with bladder control and difficulty dual tasking. Clinicians should not rely on a clinical measure of balance alone to identify falls risk but consider a multivariable model that would be more sensitive and provide more useful information. Future research should validate this falls risk model using a larger sample size, with a wider range of EDSS levels and disease subtypes. Following validation, implementation could be carried out and if used successfully in daily clinical practice this model could help prioritise waiting lists and enable earlier access to fall prevention interventions at the most appropriate time point for that individual.

Declaration

I declare that this doctoral thesis is entirely my own work and that it has not been submitted at this or any other University or higher education institution for any academic award.

Signature: _____

Gillian Quinn

Table of Contents

Abstract	i
Declaration	ii
Acknowledgements	vii
List of Tables.....	ix
List of Figures	xi
List of Appendices	xiii
List of Abbreviations.....	xiv
List of Publications Arising From this Thesis.....	xvi
Thesis Outline	xviii

Chapter 1 - Introduction

Prevalence and Symptoms of MS	2
Prevalence of Falls in MS	3
Defining Falls and Fallers	4
Consequences of Falls in MS	5
Risk Factors Associated with Falls in MS	8
Balance Assessment using the TUG	11
Dual Task Cost and Association with Falls Risk	12
Identification of Risk and Treatment Prioritisation	13
Risk Prediction	14

Objectives of the Thesis.....	16
-------------------------------	----

References.....	17
-----------------	----

Chapter 2 - The Ability of Clinical Balance Measures to Identify Falls Risk in Multiple Sclerosis; a Systematic Review and Meta-Analysis

Contribution.....	26
-------------------	----

Abstract.....	27
---------------	----

Introduction.....	29
-------------------	----

Methods.....	30
--------------	----

Results.....	34
--------------	----

Discussion.....	47
-----------------	----

Conclusion.....	51
-----------------	----

References.....	52
-----------------	----

Chapter 3 - Discriminative Ability and Clinical Utility of the Timed Up and Go, TUG, in Identifying Falls Risk in people with Multiple Sclerosis; a Prospective Cohort Study

Contribution.....	59
-------------------	----

Abstract.....	60
---------------	----

Introduction.....	62
-------------------	----

Methods.....	64
--------------	----

Results.....	68
--------------	----

Discussion	72
Conclusion	77
References	78

Chapter 4 - An Exploration of Falls and Dual Tasking; a prospective cohort study of people with Multiple Sclerosis

Contribution	83
Abstract	84
Introduction	85
Methods.....	88
Results	93
Discussion	98
Conclusion	103
References	104

Chapter 5 - Development of a Falls Risk Prediction Tool for people with Multiple Sclerosis

Contribution	111
Abstract	112
Introduction	113
Methods.....	115
Results	120

Discussion	125
Conclusion	129
References	131

Chapter 6 - Exploration of the Variance of the Model

Introduction	136
Methods	137
Results	141
Discussion	155
Conclusion	160
References	161

Chapter 7 - Discussion

Introduction	166
Key Findings of the Thesis	166
Considerations for Clinical Practice	172
Considerations for Future Research	176
Methodological Issues	184
Limitations of the Thesis	192
Methodological Considerations for Future Studies	194
Conclusion	199
References	201

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List of Tables

Table 2.1a: Methodological Quality of Prospective Cohort Studies.....	38
Table 2.1b: Methodological Quality of Cross-Sectional Studies	39
Table 2.2: Discriminative Ability and Clinical Utility of Clinical Measures in Prospective Cohort Studies	42
Table 3.1: Comparison of Demographic Information and Clinical Characteristics of Fallers (≥ 1 fall) and Non-faller (0 falls) with Multiple Sclerosis	69
Table 3.2: The AUC, Sensitivity and Specificity, Predictive Values and Likelihood Ratios for the TUG and TUG-Cognitive.....	70
Table 3.3: 2 X 2 Table for Timed Up and Go with a Cut Point of 9 seconds and a Faller Classification of ≥ 1 fall.....	70
Table 4.1: Comparison of Demographic Information and Clinical Characteristics of Fallers and Non-Fallers with Multiple Sclerosis	94
Table 4.2: Comparison of TUG, TUG-C and DTC scores of people with Multiple Sclerosis based on prospective falls status where faller = person with ≥ 2 falls	95
Table 4.3: Comparison of Self-reported Problems Dual tasking between Fallers and Non-fallers, where faller = person with ≥ 2 falls.....	96
Table 4.4: Between-group comparison of Percentage of Fallers (person with ≥ 2 falls) and Non-fallers Based on Pattern of CMI (n= 88, not assessed for first 12 participants. Some participants used more than one pattern, n= 2 used 2 patterns, n= 1 used 3 patterns)	97
Table 5.1: Demographic and Clinical Information for the Sample	121
Table 5.2: Full Model for Logistic Regression Analysis (n=100) to Predict Fallers	123

Table 5.3: Logistic Regression Analysis, Final Model (n=100) to Predict Fallers	124
Table 6.1: Discriminative Ability, Clinical Utility and Odds Ratios of Clinical and Instrumented Measures of Mobility and Balance	143
Table 6.2: Discriminative Ability, Clinical Utility and Odds Ratios of Self Report Variables and Previous models	146
Table 6.3: Discriminative Ability, Clinical Utility and Odds Ratios of Cognitive and Medication Related Variables	148
Table 6.4: Participant Demographics for Clinician Interviews.....	152

List of Figures

Figure 2.1: Flow of Studies Screened for Inclusion in the Review	35
Figure 2.2a: Mean Difference in Berg Balance score between Fallers and Non-fallers.....	44
Figure 2.2b: Mean Difference in Dynamic Gait Index between Fallers and Non-fallers.....	44
Figure 2.2c: Mean Difference in Timed Up and Go between Fallers and Non-fallers.....	45
Figure 2.2d: Mean Difference in Timed Up and Go-Cognitive between Fallers and Non-fallers.....	45
Figure 2.2e: Mean Difference in Mini-BESTest score between Fallers and Non-fallers.....	46
Figure 2.2f: Mean Difference in Four Square Step test score between Fallers and Non-fallers.....	46
Figure 2.3a: Mean Difference in Activities Specific Balance Confidence scale between Fallers and Non-fallers.....	47
Figure 2.3b: Mean Difference in Falls Efficacy Scale International score between Fallers and Non-fallers	47
Figure 3.1: Receiving Operating Curve Analysis for Timed Up and Go (TUG) and Timed Up and Go Cognitive (TUG-Cog) in Predicting Fallers (≥ 1 fall) in Multiple Sclerosis.....	71
Figure 3.2: Receiving Operating Curve Analysis for Timed Up and Go (TUG) and Timed Up and Go Cognitive (TUG-Cog) in Predicting Fallers (≥ 2 falls) in Multiple Sclerosis.....	71

Figure 4.1: Cognitive Motor Interference (CMI) Patterns Utilised Amongst	
Whole Group.....	97
Figure 5.1: Receiving Operating Curve Analysis (ROC) of the Final Model,	
AUC = 0.72	124

List of Appendices

Appendix 2.1 MOOSE Checklist for Meta-Analysis of Observational Studies	215
Appendix 2.2 Search Strategy	217
Appendix 2.3 Descriptive Characteristics of Prospective Cohort Studies	219
Appendix 2.4 Descriptive Characteristics of Cross-Sectional Studies	226
Appendix 5.1 TRIPOD Checklist, Prediction Model Development	241
Appendix 5.2 Falls Screening Questionnaire	243
Appendix 5.3 Data Collection Tool for Prospective Cohort Study	244
Appendix 5.4 Variables for Inclusion in Model; 20 potential Predictor Variables with a p value ≤ 0.2 after Bivariate Analysis	251
Appendix 6.1 Falls Diary	253

List of Abbreviations

ABC- activities specific balance confidence scale

AUC- area under the receiving operating curve characteristic

BBS- berg balance scale

CFIR- consolidated framework for implementation research

CMI – cognitive motor interference

CNS – central nervous system

DGI – dynamic gait index

DTC- dual task cost

EDSS – expanded disability status scale

EMTReK- evidence based model for the transfer and exchange of research knowledge

FEM- fixed effects model

FESI - falls efficacy scale international

HSE – health service executive

IMSFPRN – international multiple sclerosis falls prevention research network

KTE- knowledge transfer exchange

MOOSE- meta-analysis of observational studies in epidemiology

MS- multiple sclerosis

MSWS-12 – 12 item multiple sclerosis walking scale

PARiHS- promoting action on research implementation in health services

PPA – physiological profile assessment

ProFaNE – prevention of falls network Europe

REM- random effects model

RRMS- relapse remitting multiple sclerosis

SDMT – symbol digit modalities test

STROBE- strengthening the reporting of observational studies in epidemiology

TRIPOD- transparent reporting of a multivariable prediction model for individual prognosis or diagnosis

TUG- timed up and go

TUG-C – timed up and go cognitive

T25FW – timed 25-foot walk

List of Publications Arising from this Thesis

Published/Accepted for Publication -

1. Quinn, G., Comber, L., Galvin, R., Coote, S. (2017) 'The ability of clinical balance measures to identify falls risk in Multiple Sclerosis: a systematic review and meta-analysis', *Clinical Rehabilitation (Q1 rehabilitation, Impact Factor:2.93)*
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3. Quinn, G., Comber, L., O'Malley, N., McGuigan, C., Galvin, R., Coote, S. (2018) 'An Exploration of Falls and Dual Tasking; a prospective cohort study of people with Multiple Sclerosis', *Topics in Geriatric Rehabilitation (Q3 rehabilitation, Impact Factor:0.46)*

Published Conference Abstracts –

1. Quinn, G., Comber L., Galvin, R., McGuigan, C. and Coote, S. (2016) 'Exploring Dual Task Cost in People with Multiple Sclerosis; the Relationship to Falls Status and Cognitive Function' *Multiple Sclerosis Journal*, 22(s3), 439 ECTRIMS 2016 Poster Abstract (*Q1 neurology, Impact Factor: 5.28*).
2. Quinn, G., Comber L., Galvin, R., McGuigan, C. and Coote, S. (2016) 'Assessing the Predictive Validity of the TUG, Timed Up and Go Test, and a Falls Screening

Questionnaire to Determine the Risk of Falling in People with Multiple Sclerosis', International Journal of MS Care, 18(s1) CMSC 2016 Poster Abstract (*Q3 neurology*).

3. Quinn, G., Comber L., Galvin, R., McGuigan, C. and Coote, S. (2016) 'Falls in People with MS, Causes, Attributions and Intervention Needs' International Journal of MS Care, 18(s1) CMSC 2016 Poster Abstract (*Q3 neurology*).

Thesis Outline:

This thesis is a traditional thesis where each chapter is in the form of a research paper, framed by an introduction and discussion chapter. There are seven chapters in total, of which four (chapters 2-5) are papers that have either been published, are under review or accepted for publication in peer reviewed journals. The first chapter is the introduction, the second chapter is a systematic literature review and meta-analysis examining current clinical measures of balance and their use in identifying falls risk in Multiple Sclerosis (MS), the third chapter examines the discriminative ability and clinical utility of the Timed Up and Go (TUG) and TUG-cognitive, the fourth chapter examines the association between dual task cost and falls in people with MS, the fifth chapter explains how the final falls risk model was developed and reports on its sensitivity and discriminative ability, the sixth chapter examines further potential factors that may explain the variance of the model and the final chapter comprises a discussion and conclusion.

Chapter 1:

Introduction

This introduction chapter will give background information about the topic being investigated i.e. the development of a falls risk screening tool for use in Multiple Sclerosis (MS). The points for consideration in this chapter include the prevalence and monitoring of falls in MS, the consequences of falls in this population, the known risk factors associated with falls in MS and the importance of identifying those at risk of falls to enable earlier falls prevention interventions. Certain risk factors such as balance impairment and cognitive impairment will be examined more closely and the assessment of these variables in relation to falls risk will be discussed. The clinical context in relation to identification of risk and treatment prioritisation will be explored, as will certain methodological aspects regarding risk prediction such as discriminative ability and clinical utility. The introduction will conclude with the aims and objectives of the thesis.

Prevalence and symptoms of MS-

MS is the leading cause of disability in young and middle-aged people in the developed world with a global prevalence of 33 per 100,000 and a total of 2.3 million people with MS worldwide making it one of the most common neurological disorders in young adults (Koch-Henriksen and Sørensen 2010; Browne *et al.* 2014). There are over 9,000 people with MS living in Ireland with a societal cost of 429 million euro per year (Carney *et al.* 2018) including direct medical and non-medical costs and indirect costs such as productivity losses due to sick leave, inability to maintain gainful employment and early retirement. MS typically has a very heterogeneous presentation with a wide range of systems affected by the disease including balance, co-ordination, muscle tone, sensation, cognition and vision. The range of symptoms and impairments

present will vary depending on the location of lesions within the central nervous system (CNS). The most common clinical symptoms reported when first attending a healthcare professional include sensory (40% of people with MS present with numbness, tingling, burning pain), motor (39% present with weakness, stiffness, altered coordination), visual (30%) and fatigue (30% present with an overwhelming lack of physical or mental energy that interferes with daily activities) (*Multiple Sclerosis International Federation, 2013. Atlas of MS 2013: Mapping Multiple Sclerosis around the World.*). Although the CNS has some potential for recovery and repair, this repair is often incomplete and results in irreversible damage and concurrent brain atrophy (Rocca *et al.* 2003). This brain atrophy starts early, proceeds throughout the course of the disease and accelerates at a much faster rate than seen in people without MS (De Stefano *et al.* 2010).

Prevalence of falls in MS-

These common motor and sensory impairments may alter an individual's gait and mobility performance and are often associated with fall risk (Peterson *et al.* 2007; Sosnoff *et al.* 2011). Falls are prevalent in this population with a large multi-site study (n= 537) that combined data from four different countries demonstrating 56% fall at least once within a three month period and of those fallers 37% are frequent fallers reporting two or more falls, with a total of 1721 falls reported over the three month study period (Nilsagård *et al.* 2015). In smaller studies even higher rates of falling have been reported with Gunn et al (n= 148) reporting 70% having one or more falls with a total of 672 falls over a three month period (Gunn *et al.* 2013a), Cameron et al reporting 71% fallers (2013) and Tijmsa et al reporting 60% fallers, of which 55% had

3 or more falls (2017). The latter two studies both had longer follow up periods of prospective falls monitoring for 6 months. People with MS fall more, are more likely to suffer injurious falls and have different fall circumstances compared to their healthy peers, with 71% of people with MS falling versus 41% of healthy controls over a 6-month study period (Mazumder *et al.* 2014).

Defining falls and fallers in MS-

In research to date on falls in MS there are a variety of faller classifications utilised with some researchers defining a faller as a person with 1 or more falls (Nilsagård *et al.* 2009b; Coote *et al.* 2013; Ytterberg *et al.* 2013) and other researchers defining fallers on the basis of two or more falls (Gunn *et al.* 2013a; Hoang *et al.* 2016a; Kalron and Allali 2017). Likewise there is a wide range of fall definitions utilised; with some defining a fall as ‘an unexpected event that results in the person ending up on the ground, floor, or any lower surface’ (Cameron *et al.* 2013; Forsberg *et al.* 2016; Tajali *et al.* 2017), others defining it as ‘unintentionally coming to the ground or other lower level and other than a consequence of sustaining a violent blow, loss of consciousness, sudden onset of paralysis as in stroke or epileptic or seizure’ (Hoang *et al.* 2016a) and still others defining it ‘as any unexpected loss of balance that resulted in whole body contact with the ground’ (Kasser *et al.* 2014). In some studies the fall definition used is not stated (Jacobs and Kasser 2012; Kalron 2016). This heterogeneity in fall definition and classification can make comparison between studies difficult. The International MS Falls Prevention Research network (IMSFPRN) has recommended prospective monitoring of falls using falls diaries for a minimum three-month period, that fallers be classified as participants experiencing one or more falls during the study

period and a fall be defined as ‘an unexpected event in which the participant comes to rest on the ground, floor or lower level’ as used by the Prevention of Falls Network Europe (ProFaNE) (Coote *et al.* 2014).

Consequences of falls in MS-

The consequences of falls for people with MS are far reaching and can have a significant societal and personal impact. Injurious falls are highly prevalent with previous cross-sectional studies with large cohorts surveyed reporting injurious falls rates of 34-50% and that fear of falls and osteoporosis are significantly associated with injurious falls requiring medical attention (Peterson *et al.* 2008; Matsuda *et al.* 2011). A population based cohort study found that people with MS have a threefold higher risk of hip fracture than age and gender matched peers with a greater risk for those prescribed steroids in the previous six months (Bazelier *et al.* 2011). Three studies using prospective falls reporting have reported on injurious fall rates over a six month follow-up period with rates varying from 42-58% (Cameron *et al.* 2013; Hoang *et al.* 2014; Mazumder *et al.* 2014). Injurious falls can result in increased healthcare utilisation and decreased labour force productivity which both contribute to the high socio-economic cost associated with MS (Carney *et al.* 2018). These high rates of injurious falls are much greater than those seen in the elderly where rates of 23% (Welmer *et al.* 2017) to 30% (Pohl *et al.* 2014) have been reported and post stroke where rates of 10% have been reported (Tilson *et al.* 2012).

People with MS who are experiencing worsening mobility and more progressive disease are at a higher risk of falls (Nilsagård *et al.* 2015), which may result in increased healthcare utilisation; not just for the management of injurious falls but for physiotherapy or occupational therapy falls prevention interventions and for home adaptations and carer support. The total societal cost of MS includes direct medical and non-medical costs, as well as intangible costs and in Europe the overall annual cost has been estimated at 15.5 billion euro (Kobelt *et al.* 2006). In Ireland, a report published by the MS Society of Ireland demonstrated the overall annual societal cost attributable to MS is 429.15 million euro and there is a direct relationship between healthcare resource use and disability severity, with costs increasing as disability progresses (Carney *et al.* 2018). Of the nationally representative sample (n= 594) surveyed for the Irish report, 40% of respondents utilised physiotherapy, 16% utilised occupational therapy, 25% had home adaptations and 16% had some form of home help/carer.

On a personal level the high rate of falls and high levels of fear of falling experienced by a person with MS may lead to activity curtailment and further reductions in physical fitness and endurance (Peterson *et al.* 2007; Matsuda *et al.* 2012). Fear of falling is defined as “a lasting concern about falling that results in an individual avoiding activities that he/she remains capable of performing” (Tinetti and Powell 1993). Previous studies in MS have shown a very high level of fear of falling with 63.5% of a large study cohort (N= 1064) reporting fear of falling and 82% of that group curtailing their activities because of that fear (Peterson *et al.* 2007). In contrast to physical variables, psycho-social variables such as fear of falling and low falls self-efficacy tend to receive less attention in falls prevention interventions, despite being

common among people with MS who have experienced falls (Comber *et al.* 2017). Comber et al found that 92% of their cross-sectional sample expressed fear of falls with an associated curtailment of activities seen in 79% of respondents and a significant correlation demonstrated between falls self-efficacy (scored on the Falls Efficacy Scale international (FESI)) and the number of falls. Falls self-efficacy, defined as one's perceived sense of control over falling, has been shown to be an important mediating factor on fear of falling and when measured using the FESI has been shown to be significantly associated with future recurrent falls in a longitudinal study (Mazumder *et al.* 2015). Recent research has shown a significantly slower gait speed in non-fallers with fear of falling in comparison to fearless fallers (Kalron and Allali 2017) and highlights the fact that fear of falling may be just as limiting as actual falls and is a construct worth examining in further detail.

Previous cross-sectional data from people with MS who use a mobility aid demonstrated a lower quality of life in fallers (Coote *et al.* 2013) and prospective data from a larger study cohort has shown that greater fear of falls is associated with a greater risk of falls and lower quality of life (Vister *et al.* 2017). Lower quality of life, in turn has higher associated socio-economic costs, and contributes significantly to the intangible costs and burden for the person with MS related to issues around self-care, pain, anxiety and depression (Carney *et al.* 2018).

Having a chronic progressive condition such as MS places a significant burden on the individual and the unmet needs of people with this condition have been highlighted in previous studies. Limited access to physiotherapy services for those requiring

neurological rehabilitation has been demonstrated in Australia with an imbalance between increasing service demands and limited physiotherapy capacity (Adams *et al.* 2015). In the UK, a survey of people with MS demonstrated that advice about exercise was the most requested information source (Somerset *et al.* 2001) and that lack of information about physiotherapy services and excessive waiting list times was one of the most negative aspects of their overall management (Markwick *et al.* 2014). In a profiling study of physiotherapy services for people with MS in Ireland it was found there was a very short duration of physiotherapy received (mean of 3.6 hours) (Coote *et al.* 2010), far less than the 8-12 hours received by participants in studies that have demonstrated positive benefits of physiotherapy and exercise interventions (Cattaneo *et al.* 2007; Hoang *et al.* 2016b; Hugos *et al.* 2016). A more recent study exploring the unmet needs of people with MS in Ireland found that 52% of the cohort reported MS related unmet needs and physiotherapy was the most frequently reported unmet need (Lonergan *et al.* 2015). A sensitive falls risk tool of the type developed in this thesis may be useful in identifying risk earlier, prioritising wait list times and enabling earlier access to physiotherapy services.

Risk factors associated with falls in people with MS-

There is a growing body of evidence examining the factors associated with falls in MS but as yet there are a limited number of studies using the gold standard method of prospective falls recording. Previous cross sectional studies have found various factors to be associated with falls including slower gait speed, impaired balance, fatigue, older age, worse disability level, increased use of assistive devices and decreased walking endurance (Sosnoff *et al.* 2011; Coote *et al.* 2013; Ytterberg *et al.* 2013). The use of

retrospective recall for falls data is a definite limitation in these studies, as is the older age group (all have a mean age of greater than 50 years) indicating findings are not applicable to a younger, milder disease cohort.

Prior to the design of the study protocol for this PhD in March 2015, the number of prospective studies examining falls risk prediction in MS was limited. Some studies explored the discriminative ability and sensitivity of clinical variables/measures alone (Nilsagård *et al.* 2009b; Dibble *et al.* 2013) and others compared clinical measures to more complex measures such as static and dynamic posturography (Cameron *et al.* 2013; Prosperini *et al.* 2013). These studies have conflicting results with some studies recommending measures such as the Berg Balance Scale for identifying falls risk (Nilsagård *et al.* 2009b; Dibble *et al.* 2013) while others report low sensitivity levels for the Berg and found static posturography to be more sensitive and accurate for identifying falls risk (Prosperini *et al.* 2013). All four studies examined the Expanded Disability Status Scale (EDSS) score and while it was shown to be significantly different between fallers and non-fallers (Prosperini *et al.* 2013) two of the studies found it to have low levels of predictive accuracy (Cameron *et al.* 2013; Dibble *et al.* 2013), while a different study found the odds of falling were doubled for each degree of increased EDSS score (Nilsagård *et al.* 2009b). Cameron *et al.* found that a history of falls was the best predictor of future falls and was just as reliable as more complex or more time consuming assessments (Cameron *et al.* 2013) but their cohort was small (n=52) and was predominantly the relapse-remitting form of MS with a younger age than other similar studies on this topic.

Still others examined the sensitivity of multivariable models that included simple clinical variables such as EDSS score, Ashworth score, reported leg pain, and slower walking speed in combination with more complicated variables that require specialist equipment such as gait analysis, strength assessment using the Biodex Multipoint System and the Physiological Profile Assessment (Kasser *et al.* 2011; Gunn *et al.* 2013a; Hoang *et al.* 2014). These falls risk prediction models have varying levels of sensitivity and specificity ranging from 48% to 81% and 56% to 88% respectively with area under the receiving operating characteristic curve (AUC) values of 0.71 and 0.73 (reported for two models (Gunn *et al.* 2013a; Hoang *et al.* 2014)). Differences in study methodology including the use of different fall definitions, different faller classifications, varying follow up time points and different outcome measures make comparison of findings difficult. More importantly few studies report both clinical utility, in the form of sensitivity and specificity, and discriminative ability in the form of AUC values together, with some studies reporting neither but instead simply examining differences between fallers and non-fallers or reporting odds ratio values. Unfortunately, this heterogeneity in methodological procedures makes study comparison difficult and limits the applicability and strength of the results.

Two recent systematic reviews have examined the combined literature in relation to factors associated with increased risk of falls in MS. The first review included 8 studies (only 2 of which used prospective falls monitoring) with a total of 1929 participants and found that impairments in balance and cognition, progressive MS and use of a mobility aid are all associated with an increased risk of falls (Gunn *et al.* 2013b). A further review with 15 studies (of which 3 used prospective falls monitoring) including 2425 participants found that in comparison to non-fallers, fallers had longer

disease duration, more progressive disease, slower gait speed, worse scores on clinical balance measures and static posturography (Giannì *et al.* 2014). However, this latter review combined both prospective and cross-sectional study data in their meta-analysis which weakens the significance of their findings. While there is no doubt that our knowledge on factors associated with falls is growing, less is known about circumstances surrounding falls and their association to commonly used clinical measures of balance and gait.

Balance assessment using the TUG-

Balance impairment is a known risk factor for falls in MS, but it is unclear whether balance measures currently in use are sensitive enough to predict those at risk of falling. Various physical tests of gait and balance and self-report questionnaires have been shown to correlate with falls risk in MS (Cattaneo *et al.* 2006; Nilsagard *et al.* 2007; Nilsagård *et al.* 2012) but it is unclear if these measures can reliably predict those at risk of falling. One clinical measure that is widely used in clinical practice to differentiate between fallers and non-fallers is the Timed Up and Go (TUG). For assessment of falls risk the TUG would appear to have good face validity as it involves walking, turning and transition from a standing to seated position which are all mobility manoeuvres previously shown to be associated with falls in people with MS (Nilsagård *et al.* 2009a; Gunn *et al.* 2014). The TUG has been recommended as a screening test for falls risk by the American Geriatrics Society/British Society of Gerontology Guidelines (2011) and has been shown to have good validity (Sebastião *et al.* 2016) and reliability (Nilsagard *et al.* 2007) in MS populations. Furthermore, the TUG is quick and easy to administer requiring no specialist training or equipment

(Podsiadlo and Richardson 1991) and is well known and commonly used by physiotherapists working in the Irish healthcare system (O' Donovan 2011). The IMSFPRN recommend that MS falls prevention studies should use measures that capture transitions and walking and that can incorporate dual tasking (Cattaneo *et al.* 2014); the TUG and TUG-Cognitive cover these suggested domains and have also been recommended for use in MS research and clinical practice by the American Physical Therapy Association Evidence Database to Guide Effectiveness task force (Potter *et al.* 2014) and are therefore investigated further in this thesis.

Dual Task Cost (DTC) and association with falls risk-

Another risk factor associated with falls in MS is cognitive impairment (Gunn *et al.* 2013b) and this symptom is prevalent in MS, present in up to 70% of people with the condition (Rao *et al.* 1991) across all disease stages and in all clinical sub types (Amato *et al.* 2006). The main type of impairments seen are slower information processing, poor sustained attention and altered working memory (Benedict *et al.* 2002) all of which are relevant when functioning in a dual task capacity with resultant cognitive-motor interference. Cognitive-motor interference (CMI) is common in MS (Leone *et al.* 2015) and refers to the decline in performance of cognitive and/or motor tasks when they are performed simultaneously (dual-task), relative to the performance of each task individually (Plummer *et al.* 2013). People with relapse remitting MS have been shown to have decreased postural stability under dual task conditions (Butchard-MacDonald *et al.* 2017) and altered gait patterns including slower velocity, altered step length, increased double support time and altered cadence (Motl *et al.* 2014; Leone *et al.* 2015). The deterioration in performance associated with CMI is

expressed as dual-task cost (DTC) (Wajda and Sosnoff 2015) and has been shown to be associated with falls in people with MS (Wajda *et al.* 2013; Etemadi 2016). In elderly populations DTC has been examined as a potential predictor of falls (Yamada *et al.* 2011; Muir-Hunter and Wittwer 2016) with deterioration in gait during dual tasking specifically associated with falls risk. Thus, DTC is a potential variable warranting further investigation in relation to falls risk in MS.

Identification of risk and treatment prioritisation-

As falls are a significant problem for people with MS, with detrimental consequences and negative impacts on quality of life it is imperative to try and provide falls prevention interventions at the most appropriate time when falls risk is becoming apparent and interventions may be of most benefit. Currently the healthcare system in Ireland is unequal with access to services often dependent on a person's geographical location rather than their medical need. For people with MS, access to falls prevention interventions is through the Health Services Executive (HSE) via their hospital or through their GP/primary care service or through availing of supplementary services as provided by MS Ireland (the Multiple Sclerosis Society of Ireland). Recent plans for reform within the HSE recommend timely access to all health and social care according to medical need and has a strong focus on prevention and public health (Burke *et al.* 2018). It is not yet clear from the current evidence base how to identify those at risk of falls and in need of intervention.

The IMSFPRN published recommendations on who to target for falls prevention trials and recommended having broad inclusion criteria and including people of all ages, people with and without mobility aids, people with varied levels of cognitive ability but of a sufficient level to participate in the intervention of the study and people with a history of falls (Cameron *et al.* 2014). However, on a practical level due to limited resources, clinicians need to be able to identify those at greatest risk using a simple falls risk tool and refer the most appropriate people to the intervention programmes.

Risk Prediction-

Prediction models are a useful tool for healthcare personnel to help inform decision making and provide guidance in relation to treatment options and onward referral to other services at an appropriate time point (Collins *et al.* 2015). Prediction models are tools that use a combination of predictor variables, and are inherently multivariable, to estimate the probability that an outcome will occur in an individual (Moons *et al.* 2009). Logistic regression modelling is the most widely used statistical technique for binary medical outcomes (in this case presence or absence of faller status) (Steyerberg 2009) and traditional methods for assessing the performance of prediction models include discrimination focusing on the area under the receiving operating characteristic curve statistic (AUC) value and goodness of fit statistics for calibration (Steyerberg *et al.* 2010).

Discrimination is the ability of a measure to differentiate between individuals with and without falls and is quantified using the AUC value. The larger the AUC value the

greater the predictive ability of the measure in question (Hanley and McNeil 1982). The AUC measures the average true positive rate (predicted falls that actually occurred) over all false positive rates (predicted falls that did not actually occur). The AUC can have any value between 0 and 1 with an AUC value of 0.5 representing chance, values between 0.7 and 0.9 representing moderate discrimination and a value of 1 representing perfect discrimination (Moons *et al.* 2015).

In relation to a prediction model to be used as a falls screening tool, clinical utility is assessed using the summary estimates of sensitivity and specificity. In clinical practice, balance screening tools with high sensitivity ($\geq 80\%$) are preferable to safely ‘rule-out’ those at low risk of a subsequent fall (as opposed to diagnostic tools that generally demonstrate high specificity) (Riddle and Stratford 1999). Thus, a falls risk prediction model with an AUC value of greater than 0.7 and sensitivity of greater than 80% would be acceptable to use to identify and prioritise those most in need of falls prevention interventions.

To summarise this introduction chapter; it is accepted that falls are a major problem for people with MS and have far reaching consequences that include personal, societal and economic aspects. While more is now known about risk factors associated with falls, there is currently no simple falls prediction model available that has been specifically designed for everyday clinical practice using methodological procedures that examine indices of discrimination and clinical utility in the form of AUC values and sensitivity levels. Thus, the main aim of this thesis is to develop a falls risk

assessment tool for people with MS that is suitable for use in a busy clinic setting and that demonstrates acceptable levels of discrimination and clinical utility.

The specific objectives of the thesis are to –

- 1) Summarise the totality of evidence from observational studies regarding the association between clinical assessments of balance and falls in people with Multiple Sclerosis in the form of a systematic review and meta-analysis.
- 2) Determine the sensitivity and discriminative ability of the Timed Up and Go test (TUG) and TUG-Cognitive in isolation using prospectively collected falls data.
- 3) Determine the extent of cognitive motor-interference (CMI) in fallers and non-fallers, by examining the variable of dual task cost by means of objective and subjective measures and its association with falls risk in people with MS.
- 4) Develop a simple falls risk screening tool/prediction model suitable for use in a busy clinic setting, by analysing which combination of subjective and objective variables has the highest sensitivity and predictive validity for identifying falls risk in people with MS.
- 5) Examine potential factors that may further explain the variance in the final falls prediction model using information from 1) a narrative review of the current prospective studies examining falls risk in MS, 2) data about the causes and context of falls from information collected using the falls diaries in the longitudinal study, and 3) opinions from clinicians on falls prevention interventions and assessment collected from qualitative interviews.

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Chapter 2:

The Ability of Clinical Balance
Measures to Identify Falls Risk in
Multiple Sclerosis: A Systematic
Review and Meta-Analysis

Paper Status: published in Clinical Rehabilitation

Gillian Quinn, Laura Comber, Rose Galvin, Susan Coote.

Authors' Contributions:

The author of this thesis (GQ) contributed to the paper as follows-

- Identified the research question.
- Determined the search terms and inclusion/exclusion criteria in discussion with co-author Susan Coote.
- Ran the systematic search.
- Completed data extraction.
- Assisted with the statistical analysis with co-author Rose Galvin.
- Wrote the paper and submitted for publication.

LC assisted with quality assessment of the included studies and manuscript preparation. RG assisted with statistical analysis and manuscript preparation. SC participated in study concept and design and assisted with manuscript preparation. All authors read and approved the final manuscript.

Abstract

Objective

To determine the ability of clinical measures of balance to distinguish fallers from non-fallers and to determine their predictive validity in identifying those at risk of falls.

Data Sources

AMED, CINAHL, Medline, Scopus, PubMed Central and Google Scholar.

First search: July 2015. Final Search: October 2017.

Review Methods

Inclusion criteria were studies of adults with a definite Multiple Sclerosis diagnosis, a clinical balance assessment and method of falls recording. Data were extracted independently by two reviewers. Study quality was assessed using the QUADAS-2 scale and the modified Newcastle-Ottawa Quality Assessment Scale. Statistical analysis was conducted for the cross-sectional studies using Review Manager 5. The mean difference with 95% confidence interval in balance outcomes between fallers and non-fallers was used as the mode of analysis.

Results

We included 33 studies (19 cross sectional, 5 randomised controlled trials, 9 prospective) with a total of 3901 participants, of which 1917 (49%) were classified as fallers. The balance measures most commonly reported were the Berg Balance Scale, Timed Up and Go and Falls Efficacy Scale- International. Meta-analysis demonstrated

fallers perform significantly worse than non-fallers on all measures analysed except the Timed Up and Go Cognitive ($p < 0.05$), but discriminative ability of the measures is commonly not reported. Of those reported the Activities Balance Confidence Scale had the highest AUC value (0.92), but without reporting corresponding measures of clinical utility.

Conclusion

Clinical measures of balance differ significantly between fallers and non-fallers but have poor predictive ability for falls risk in people with Multiple Sclerosis.

Introduction

Previous studies have found falls prevalence to be as high as 56% among people with Multiple Sclerosis, with 37% of those falling classed as frequent fallers (Nilsagård *et al.* 2015). Injurious falls can be serious in this group (Bazelier *et al.* 2011) and both the high rate of falls and high levels of concern about falling may lead to activity curtailment and further reductions in physical fitness and endurance (Peterson *et al.* 2007). Several factors have been shown to be associated with an increased risk of falls in Multiple Sclerosis (Giannì *et al.* 2014) including longer disease duration, more progressive disease course, use of a mobility device, slower gait speed and impaired balance. Having a balance impairment has a pooled odds ratio of 1.07 (95% CI 1.04 - 1.10) for falls among people with Multiple Sclerosis (Gunn *et al.* 2013b). While these earlier reviews (Gunn *et al.* 2013b; Giannì *et al.* 2014) have identified that impaired balance is associated with increased falls risk no systematic review to date has examined the predictive validity of the various clinical measures of balance used to identify falls risk.

A wide range of clinical tests and self-report measures have been used to evaluate balance and falls risk in Multiple Sclerosis (Cattaneo *et al.* 2006; Cattaneo *et al.* 2007; Sosnoff *et al.* 2011; Cameron and Huisinga 2013) using different observational methods. The International Multiple Sclerosis Falls Prevention Research Network (IMSFPRN) recommended the assessment of dynamic balance (Cattaneo *et al.* 2014) in falls prevention research, but it acknowledged there is not enough evidence to specifically recommend one measure over any other. Thus, the objective of this

systematic review and meta-analysis is to investigate the relationship between clinical balance measures and falls in people with Multiple Sclerosis. Firstly, we will examine if clinical balance measures demonstrate different scores in fallers and non-fallers in cross sectional studies of people with Multiple Sclerosis and secondly, we will determine the discriminative ability and clinical utility for assessing falls in prospective cohort studies. We hypothesise that there will be a significant difference between scores in fallers and non-fallers on these clinical balance measures and that measures with an area under the receiving operating curve statistic value of 0.7 or greater and a sensitivity of at least 80% will be suitable to use in identifying falls risk.

Methods

This study consists of a systematic review and meta-analysis. The Meta-analysis of Observational Studies in Epidemiology (MOOSE) (Stroup *et al.* 2000) standardised reporting guidelines were followed to ensure the standardised conduct and reporting of the research. The MOOSE checklist for meta-analyses of observational studies is available in appendix 2.1. A systematic literature search was conducted by the primary author (GQ, PhD candidate), with the first search carried out in July 2015 and the final search carried out in October 2017, and included the following databases; AMED, CINAHL, Medline (through EBSCO search platform), Scopus and PubMed Central. Keywords were formed by examining the search strategy in other systematic reviews in this area and by checking citations and keywords from results of a preliminary search in Google Scholar. The keywords and MeSH headings utilised as search terms were: ‘multiple sclerosis’ OR ‘MS’ AND ‘balance’ OR ‘postural control’ OR

‘postural instability’ OR ‘imbalance’ OR ‘stability’ AND ‘fall*’ OR ‘fall risk’. The search was supplemented through the searching of references lists of returned articles and the use of the same search terms in Google Scholar. No restrictions were placed on language or year of publication. See appendix 2.2 for more details of search strategy.

Inclusion criteria were studies of adults with a definite Multiple Sclerosis diagnosis, use of a clinical balance measure and a method of falls reporting. Cross-sectional studies were included where fallers were compared to non-fallers and prospective cohort studies were also included where balance measures were administered prior to a subsequent falls event. Baseline data from randomised controlled trials was suitable for inclusion in the meta-analysis if authors provided the relevant data when contacted and if falls were an outcome of interest in the study. Studies were excluded from this review if laboratory-based measures only were used (e.g. limits of stability using the Smart Balance Master or static posturography using force platforms) or if the cohort consisted of a mixed neurological population.

Two reviewers (GQ and SC) read the titles and/or abstracts of the identified studies and discarded irrelevant studies. Studies considered to be eligible for inclusion were read in full and their suitability for inclusion was determined independently by two reviewers (GQ, SC). Where disagreement occurred, discussions took place until consensus was reached. Authors were contacted to provide supplementary information when insufficient data were provided in the publication. If two studies were found to involve the same patient cohort, only one study was included in the meta-analysis. Information relating to authors and year of publication, study design and setting,

eligibility criteria, population demographics and outcomes of balance measures were extracted to provide summary tables.

The quality of included prospective cohort studies was assessed using the validated QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies) Scale (Whiting *et al.* 2011). The tool considers risk of bias and applicability concerns and consists of four main domains- patient selection, index test, reference standard, and flow of patients through the study including timing of the index test and reference standard. Risk of bias is judged as 'low', 'high' or 'unclear'. The quality of the cross sectional studies was assessed using the Newcastle-Ottawa Quality Assessment Scale adapted for cross sectional studies (Herzog *et al.* 2013). It involves three sub-sections: the selection of cases, the comparability of different outcome groups and the outcome itself. A star system is used to allow a semi-quantitative assessment of study quality and a maximum score of ten stars may be awarded depending on the criteria level the study meets in each section. Two of the authors (GQ and LC) independently assessed the methodological quality of the studies. Where disagreement occurred, deliberation took place until consensus was reached.

Meta-analysis of the prospective cohort studies was not possible due to the heterogeneous nature of the outcomes administered and the variability in follow-up time-points. However, the findings of these studies are summarised relating to the discriminative ability and clinical utility of the balance measures. Discrimination, the ability of a measure to differentiate between individuals with and without falls, was quantified using the area under the receiver operating characteristic curve statistic. A

value of 0.5 represents chance, values between 0.7 and 0.9 represent moderate discrimination and a value of 1 represents perfect discrimination (Moons *et al.* 2015). The clinical utility of the outcome measures was assessed using the summary estimates of sensitivity and specificity.

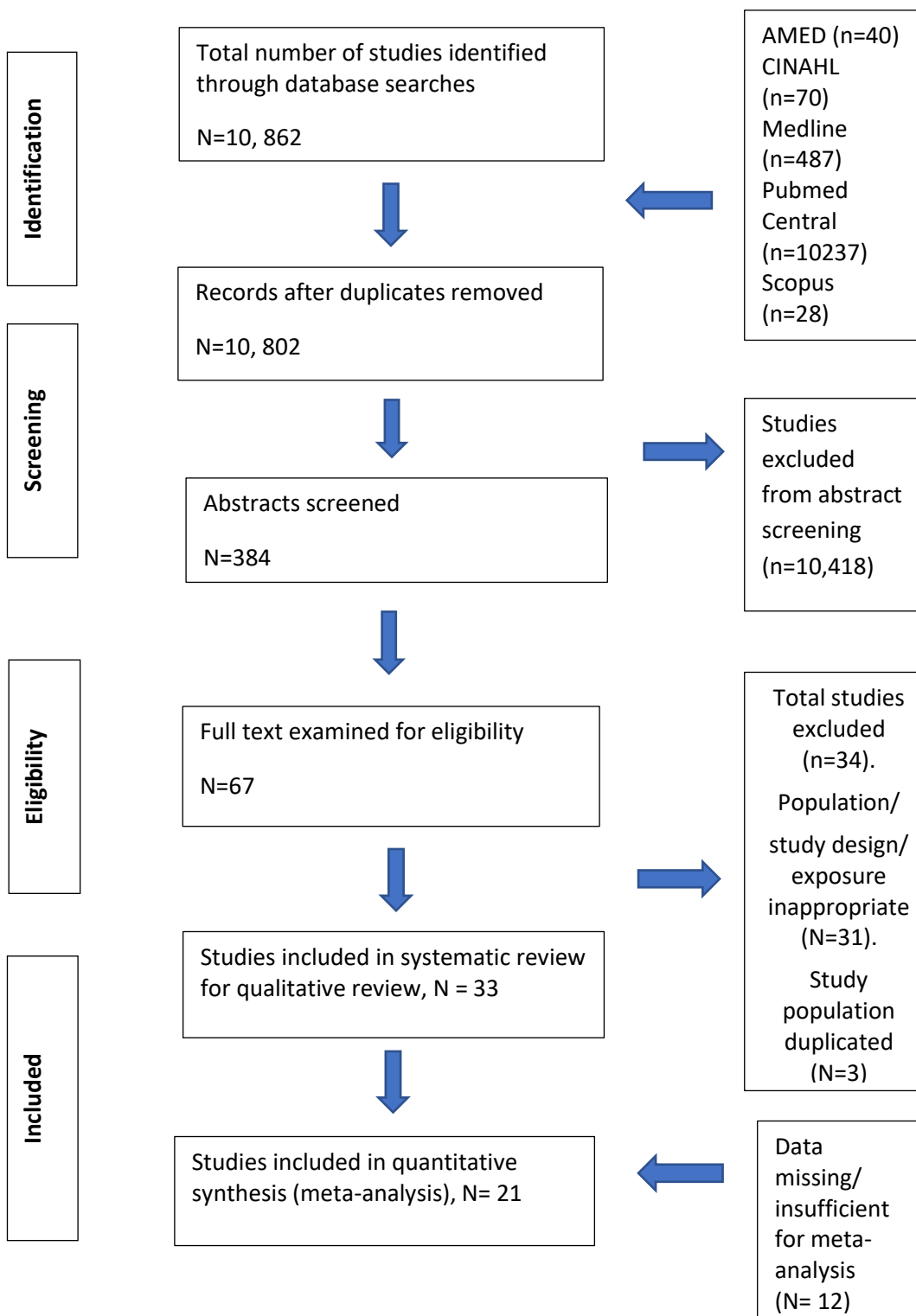
Statistical analysis was conducted for the cross-sectional studies with retrospectively collected falls data using Review Manager 5 (Version 5.3). The mean difference (MD) with 95% confidence interval in balance outcomes between fallers and non-fallers was used as the mode of analysis. We addressed the impact of sample size by estimating a weighting factor for each study and assigning larger effect-weights in studies with larger samples. Heterogeneity was examined using the I^2 statistic. We used the Cochrane interpretation of these values where an I^2 value of 30% to 60% indicates moderate heterogeneity and an I^2 of 50% to 90% demonstrates substantial heterogeneity (Ryan 2014). When the pooled data indicated moderate or substantial heterogeneity, we completed our meta-analysis using the more conservative random-effects modelling (REM) approach instead of the fixed-effects model (FEM). Where reported outcomes had a scale where a lower value is indicative of a worse outcome, the reported values were multiplied by -1 so that in all analyses a lower value indicated a better outcome (Deeks 2008).

Results

Study Selection

Figure 2.1 shows the flow of studies through the review selection process. Of the 33 studies eligible for inclusion, nine were prospective cohort studies (Cameron *et al.* 2013; Tajali *et al.* 2017; Vister *et al.* 2017) (Nilsagård *et al.* 2009; Dibble *et al.* 2013; Gunn *et al.* 2013a; Prosperini *et al.* 2013; Kasser *et al.* 2014; Hoang *et al.* 2016), 19 were cross-sectional studies (Cattaneo *et al.* 2002; Cattaneo *et al.* 2006; Sosnoff *et al.* 2011; Cattaneo *et al.* 2012; Jacobs and Kasser 2012; Nilsagård *et al.* 2012; Forsberg *et al.* 2013; Kalron and Achiron 2013; Kanekar and Aruin 2013; Ytterberg *et al.* 2013; Cameron *et al.* 2014; Kalron 2014; Ganesan *et al.* 2015; van Vliet *et al.* 2015; Kalron 2016b; Kalron 2016a; Kalron and Givon 2016; Ross *et al.* 2016; Kalron *et al.* 2017) and five were randomised controlled trials with appropriate cross sectional data (Coote *et al.* 2013; Carling *et al.* 2016; Cattaneo *et al.* 2016; Forsberg *et al.* 2016; Sung *et al.* 2016). Twelve authors were contacted for additional data, ten of whom returned data in relation to twelve different studies. Both fall definition and numbers of falls needed to be classified as a faller varied widely across the included studies with seven different fall definitions reported and two faller classifications, see appendix 2.3 and 2.4.

Figure 2.1: Flow of studies screened for inclusion in the review



A detailed summary of included studies is provided in appendix 2.3 (prospective studies) and appendix 2.4 (cross sectional studies). Within the prospective studies the participant numbers in the Multiple Sclerosis group ranged across studies from 38

(Dibble *et al.* 2013) to 416 participants (Prosperini *et al.* 2013) with a total of 1223 Multiple Sclerosis participants across the nine prospective studies. The range of mean ages reported by the prospective studies for people with Multiple Sclerosis was 30.29 years (Tajali *et al.* 2017) to 57 years (Gunn *et al.* 2013a) and six of the nine studies reported mean disease duration with averages ranging from 4.02 years (Tajali *et al.* 2017) to 14.37 years (Dibble *et al.* 2013). The mean Expanded Disability Status Scale scores ranged from 2.8 (Cameron *et al.* 2013) to 5 (Nilsagård *et al.* 2009). The duration of falls recording using falls diaries or calendars varied from 3 months (Nilsagård *et al.* 2009; Gunn *et al.* 2013a; Prosperini *et al.* 2013) to 12 months (Dibble *et al.* 2013; Kasser *et al.* 2014). The incidence of falls across these studies ranged from 41% (Prosperini *et al.* 2013) to 71% (Cameron *et al.* 2013) with a mean incidence of 56% across the nine studies.

The participant numbers in the cross sectional studies and randomised controlled trials varied from 12 (Kanekar and Aruin 2013) to 402 (Kalron 2016b) with a total number of 2,678 across the 24 studies. The mean ages reported ranged from 40 years (Kalron and Achiron 2013) to 59 years (Sung *et al.* 2016) and mean disease duration was reported in 20 of these studies with averages ranging from 4.3 years (Kalron and Achiron 2013) to 20.85 years (Carling *et al.* 2016). Expanded Disability Status Scale score was reported by 16 studies and the mean score ranged from 1.7 (Kalron and Achiron 2013; Kalron 2016a) to 6.11 (Carling *et al.* 2016). Fallers were identified using a falls history ranging from one month recall (Cattaneo *et al.* 2006) to 12 months (Sosnoff *et al.* 2011; Cameron *et al.* 2014; Kalron 2014; Ganesan *et al.* 2015; van Vliet *et al.* 2015; Kalron 2016b; Kalron 2016a; Kalron and Givon 2016; Kalron *et al.* 2017).

The prevalence of falls across these studies ranged from 23% (Cattaneo *et al.* 2012) to 76% (van Vliet *et al.* 2015), with an overall prevalence of 46%.

Balance Measures









































































Self-report balance measures utilised across all studies include the Falls Efficacy Scale International (N=9), Activities-specific Balance Confidence Scale (N=7), Dizziness Handicap Inventory (N=1) and the Survey of Activities and Fear of Falling in the Elderly (N=1). Clinical measures included the Berg Balance Scale (N=12), Dynamic Gait Index (N=6), Timed Up and Go test (N=11), Timed Up and Go cognitive (N=3), the mini BESTest (N=2), the Four Square Step test (FSST) (N=6), Lindmark Motor Capacity Assessment subscale for balance (N=1), the Balance Evaluations System Test (N=1), the Equiscale test (N=1), Functional Reach (N=1), Physiological Profile Assessment (N=2) and the Six Spot Step test (N=1). The Berg Balance Scale and Timed Up and Go were the measures most commonly used and in combination with the Activities-Specific Balance Confidence scale, Falls Efficacy Scale International, Dynamic Gait Index, Four Square Step test, Timed Up and Go Cognitive and mini BESTest provided appropriate data for meta-analysis.

Quality Assessment

A detailed overview of the methodological quality of the 33 studies is provided in Tables 2.1a (cohort studies) and 2.1b (cross-sectional studies and randomised controlled trials). In the two QUADAS-2 domains of patient selection and reference standard, all nine prospective studies showed low risk of bias in relation to

applicability, indicating an appropriate cohort was studied with a suitable method of falls recording. No study demonstrated a low risk of bias in all domains with only one study (Nilsagård *et al.* 2009) achieving a low risk of bias in six of the seven domains. The total scores on the modified Newcastle Ottawa Scale ranged from 3 stars (Cameron *et al.* 2014) to 8 stars (Cattaneo *et al.* 2002; Coote *et al.* 2013) across the cross-sectional studies. One of the studies was classified as high risk of bias (1-3 stars) (Cameron *et al.* 2014) and nine of the studies (14%) were medium risk (4-5 stars) with the remaining fourteen studies (81%) classed as low risk of bias (6-9 stars).

Table 2.1a: Methodological quality of prospective cohort studies

Study ID	RISK OF BIAS				APPLICABILITY CONCERNS			OVERALL RISK OF BIAS
	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD	FLOW AND TIMING	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD	
Cameron 2013								
Dibble 2013								
Gunn 2013								
Hoang 2016								
Kasser 2014								
Nilsagard 2009								
Prosperini 2013								
Tajali 2017								
Vister 2017								

 Low Risk  High Risk  Unclear Risk

Table 2.1b: Methodological quality of cross-sectional studies

Study ID	Selection 1, Representativeness of the sample	Selection 2, Sample size	Selection 3, Non- respondents	Selection 4, Ascertainment of the exposure	Comparability, Controls for the most important factor	Comparability, Controls for any additional factor	Outcome 1, Assessment of the outcome	Outcome 2, Statistical test	Total (out of 10)
Cameron 2014		*		**					3
Carling 2016		*		**			*	*	5
Cattaneo 2002	*	*		**	*	*	*	*	8
Cattaneo 2006	*	*		**			*	*	6
Cattaneo 2012	*			**			*	*	5
Cattaneo 2016	*	*	*	**			*	*	7
Coote 2013	*	*		**	*	*	*	*	8
Ganesan 2015	*			**			*	*	5
Forsberg 2013	*	*	*	**			*	*	7
Forsberg 2016	*	*	*	**			*	*	7
Jacobs 2012	*			*			*	*	4
Kalron 2013	*	*		**	*		*	*	7
Kalron 2014		*	*	**	*		*	*	7
Kalron 2016 (Vertical GRF)		*		**			*	*	5
Kalron 2016		*		**			*	*	5

(Validity FSST)																		
Kalron 2016 (Walk Ratio)								**					*			*		5
Kalron 2017								**					*			*		5
Kanekar 2013	*							**			*		*			*		7
Nilsagard 2012	*							**					*			*		5
Ross 2016	*			*				**					*			*		7
Sosnoff 2011	*			*				**			*		*			*		7
Sung 2016	*			*				**					*			*		6
Van Vliet 2015	*			*				**					*			*		6
Ytterberg 2013	*			*				*			*		*		*	*		7

In relation to the discriminative ability of the clinical measures, Table 2.2 presents the results of the studies. Only two studies reported the area under the receiving operating characteristic curve statistic, the sensitivity, specificity and cut off value (Hoang *et al.* 2016; Vister *et al.* 2017). Of the ten clinical balance measures investigated in the cohort studies, the Berg Balance Scale was one of the most commonly reported measures and was the only measure with both an area under the receiver operating characteristic curve statistic value of greater than 0.7 (Dibble *et al.* 2013) and a sensitivity of greater than 80% (Nilsagård *et al.* 2009). However, another study reported a conflicting sensitivity score for the Berg Balance Scale of 32% (Prosperini *et al.* 2013). The other two measures with reported area under the receiver operating characteristic curve statistic values of greater than 0.7 were the Activities-specific Balance Confidence Scale and The Falls Efficacy Scale International (Tajali *et al.* 2017) but with no corresponding sensitivity or specificity values.

Table 2.2: Discriminative Ability and Clinical Utility of Clinical Measures in Prospective Cohort Studies

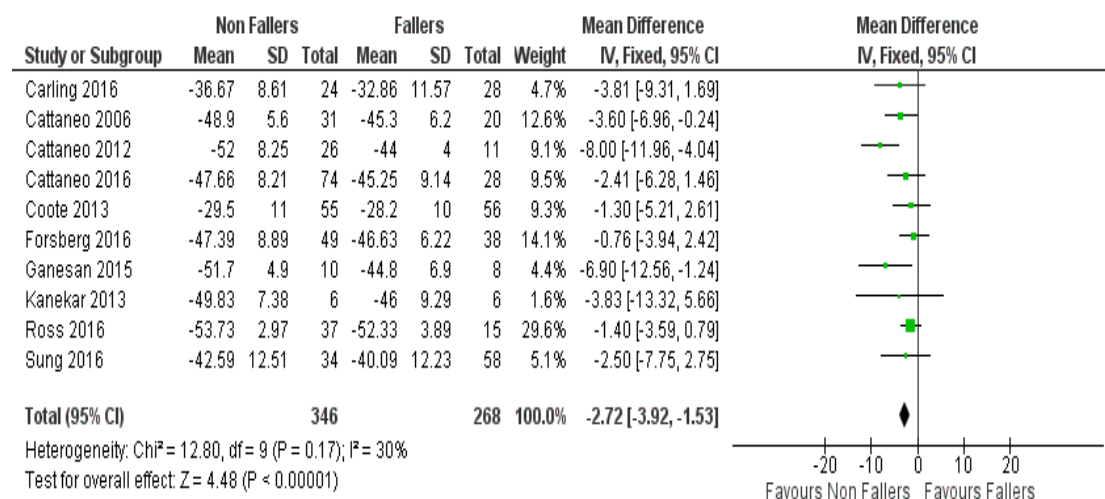
Study ID	Clinical Measure	AUC Value	Sensitivity	Specificity	Cut Off Value
Cameron 2013	Activities Balance Confidence Scale	0.69 (p = 0.02)	NR	NR	NR
	Falls Efficacy Scale International	0.66 (p = 0.03)	NR	NR	NR
Dibble 2013	Activities Balance Confidence Scale	0.68 (0.48-0.87)	NR	NR	NR
	Berg Balance Scale	0.72 (0.52-0.89)	NR	NR	NR
	Timed Up and Go	0.66 (0.46-0.86)	NR	NR	NR
	Functional Reach Test	0.66 (0.47-0.84)	NR	NR	NR
	Dynamic Gait Index	0.68 (0.49-0.87)	NR	NR	NR
Gunn 2013	Physiological Profile Assessment	0.67 (0.58-0.76)	56%	74%	NR
Hoang 2016	Physiological Profile Assessment	0.64	62%	62%	2.0
Kasser 2014	Survey of Activities and Fear of Falling in the Elderly	NR	NR	NR	NR
Nilsagard 2009	Four Square Step Test	NR	60%	75%	≥ 16.9
	Timed up and Go Cognitive	NR	73%	54%	≥ 13.6
	Berg Balance Scale	NR	94%	32%	≤ 55
Prosperini 2013	Berg Balance Scale	NR	32% (18-48)	87% (75-94)	≥ 44

Tajali 2017	Falls Efficacy Scale International	0.89 (p < 0.0001)	NR	NR	NR
	Timed Up and Go	0.65 (p = 0.014)	NR	NR	NR
	Activities Balance Confidence Scale	0.92 (p < 0.0001)	NR	NR	NR
Vister 2017	Physiological Profile Assessment	0.60	57%	60%	2.00
	Falls Efficacy Scale International	0.66	72%	53%	30

AUC = area under the receiver operating characteristic curve statistic, NR = not reported. The p value or 95% confidence interval is given in brackets after the value, where reported.

Meta-analysis of Cross-Sectional Studies-

Results of the meta-analysis for clinical measures are displayed in Figure 2.2a. Ten studies used the Berg Balance Scale (Berg *et al.* 1989) to compare balance across fallers and non-fallers (Cattaneo *et al.* 2006; Cattaneo *et al.* 2012; Coote *et al.* 2013; Kanekar and Aruin 2013; Ganesan *et al.* 2015; Carling *et al.* 2016; Cattaneo *et al.* 2016; Forsberg *et al.* 2016; Ross *et al.* 2016; Sung *et al.* 2016). Fallers demonstrated significantly lower balance scores than their counterparts without a history of falls, as presented in Figure 2a (FEM, MD = 2.72, 95% CI {1.53-3.92}, P<0.01, I² = 30%). Three of the studies (Cattaneo *et al.* 2012; Ganesan *et al.* 2015; Carling *et al.* 2016) included in the meta-analysis for this measure had an overall medium risk of bias based on methodological quality- score, the other eight were deemed low risk of bias (Newcastle Ottawa Scale score of 6 to 8).

Figure 2.2a: Mean difference in Berg balance score between Fallers and Non-Fallers

The Dynamic Gait Index (DGI) (McConvey and Bennett 2005) was used in five studies (Cattaneo *et al.* 2006; Cattaneo *et al.* 2012; Nilsagård *et al.* 2012; Forsberg *et al.* 2013; Cattaneo *et al.* 2016). The findings from these pooled studies (Figure 2.2b) demonstrate that fallers report significantly lower DGI scores than non-fallers and two (Cattaneo *et al.* 2012; Nilsagård *et al.* 2012) of the five studies included had a medium risk of bias. Five of the nine studies included in meta-analysis for the Timed Up and Go (Podsiadlo and Richardson 1991) had a medium risk of bias, with the remaining studies demonstrating a low risk of bias and the pooled meta-analysis did demonstrate a significant difference between fallers and non-fallers on this measure (Figure 2.2c).

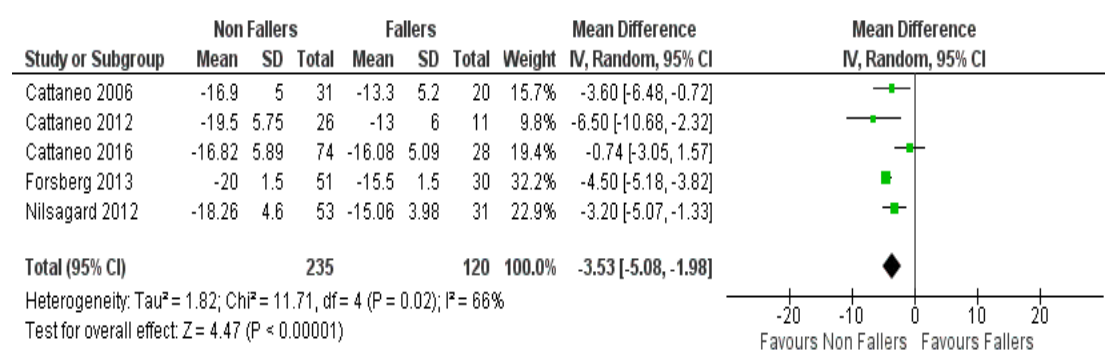
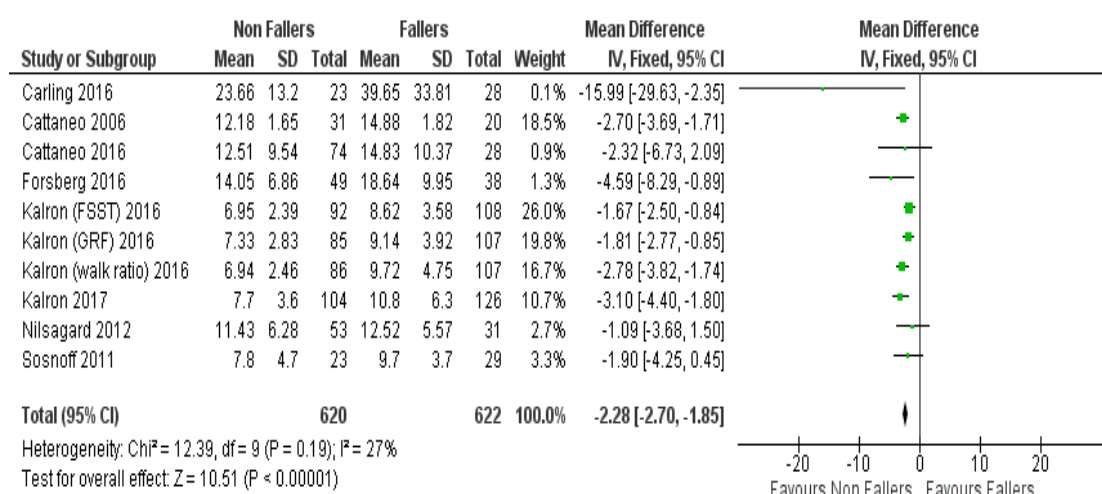
Figure 2.2b: Mean difference in Dynamic Gait Index between Fallers and Non-Fallers

Figure 2.2c: Mean difference in Timed Up and Go test between Fallers and Non-Fallers

Results for the Timed Up and Go Cognitive (Shumway-Cook *et al.* 2000), mini BESTest (Potter and Brandfass 2015) and Four-Square Step test (Dite W 2002) are seen in Figures 2.2d, 2.2e and 2.2f respectively. All measures showed a significant difference across fallers and non-fallers except for the Timed Up and Go Cognitive. The findings from the meta-analysis for the Timed Up and Go Cognitive, Mini BESTest and Four-Square Step test should be interpreted with caution as they had only small numbers of studies suitable for inclusion (two to four for each analysis).

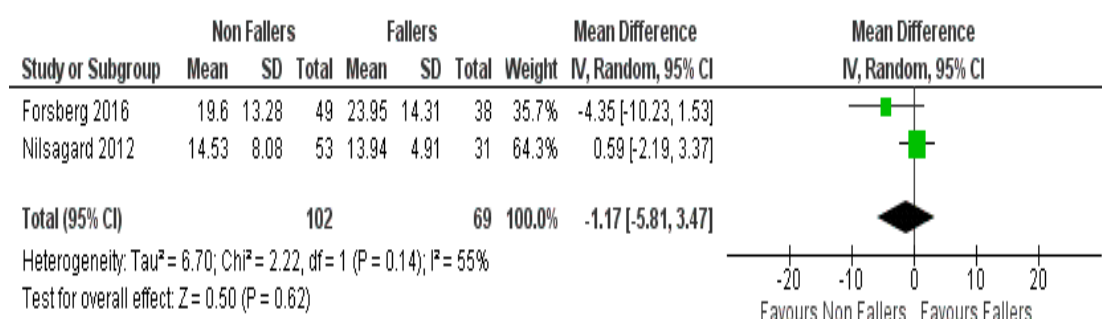
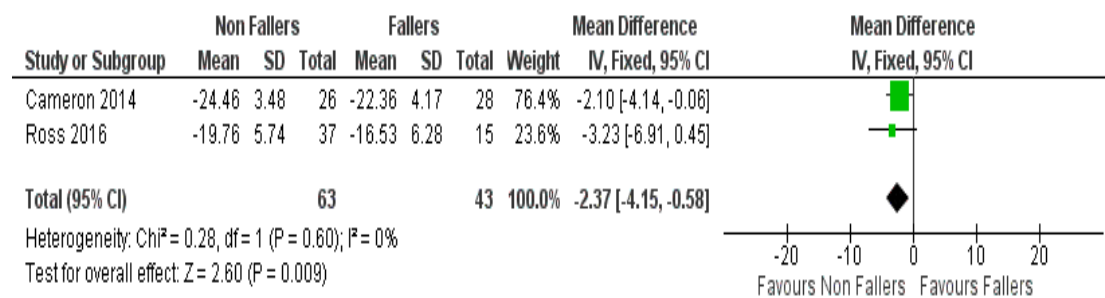
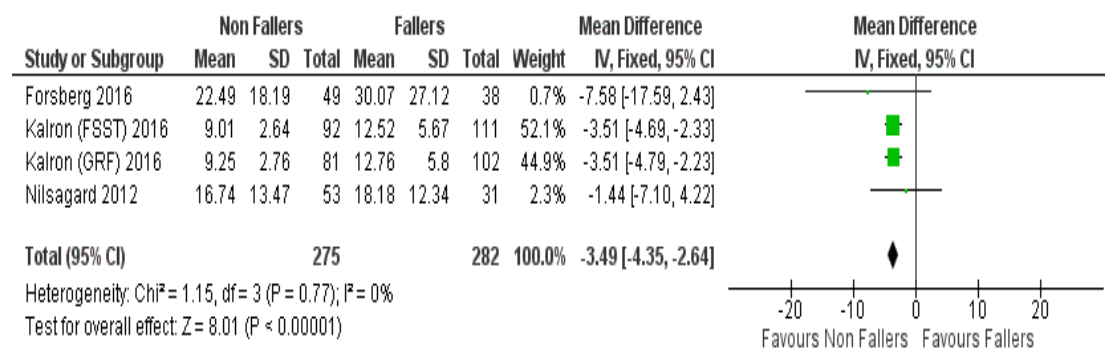
Figure 2.2d: Mean difference in Timed Up and Go Cognitive scores between Fallers and Non-Fallers

Figure 2.2e: Mean difference in Mini-BESTest scores between Fallers and Non-Fallers**Figure 2.2f: Mean difference in Four Square Step test scores between Fallers and Non-Fallers**

Findings from the meta-analysis for self-report measures, the Activities Specific Balance Confidence Scale (Powell and Myers 1995) and the Falls Efficacy Scale International (Yardley *et al.* 2005) are seen in Figure 2.3a and 2.3b. A significant difference across fallers and non-fallers was noted for both these measures. The meta-analysis for both these measures included one study with an overall medium risk of bias and this must be remembered when interpreting the results.

Figure 2.3a: Mean difference in Activities Specific Balance Confidence Scale between Fallers and Non-Fallers

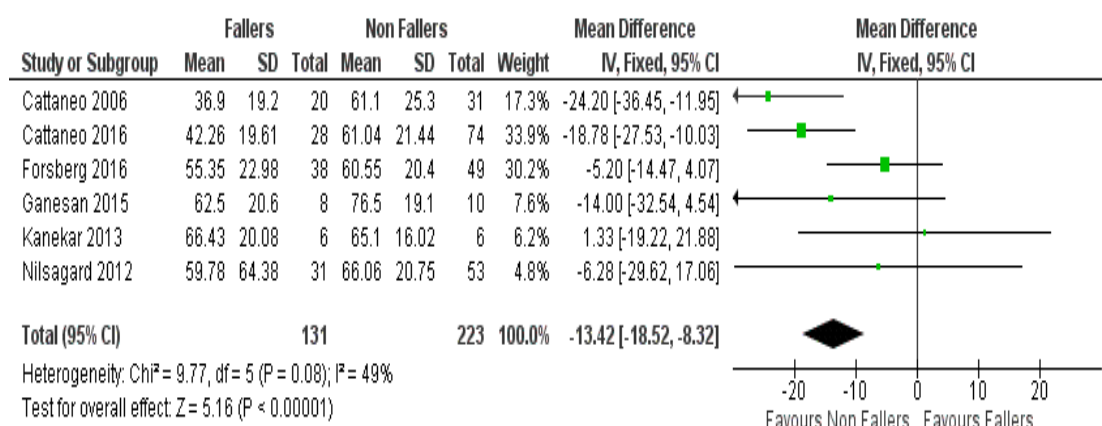
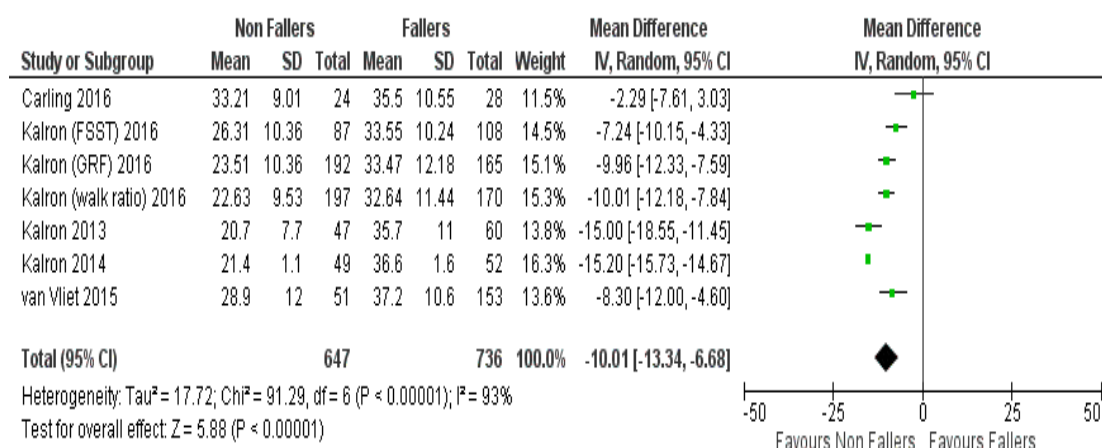


Figure 2.3b: Mean difference in Falls Efficacy Scale International between Fallers and Non-Fallers



Discussion

In this review exploring the differences in balance between fallers and non-fallers with Multiple Sclerosis and the discriminative ability and clinical utility of clinical balance measures for falls prediction, we found a total of 33 studies suitable for inclusion. The most commonly reported clinical measures were the Berg Balance Scale, the Timed

Up and Go, Activities-specific Balance Confidence Scale and Falls Efficacy Scale International. These measures do demonstrate a significant difference between fallers and non-fallers but have conflicting sensitivity values reported and often no area under the receiver operating characteristic curve statistic value reported or poor discriminative ability demonstrated. There is currently insufficient evidence from the nine prospective studies to support any balance measure as a falls prediction tool for people with Multiple Sclerosis.

From the limited number of prospective studies, there were only three reported measures demonstrating an area under the receiver operating characteristic curve statistic value of moderate discrimination; the Activities-specific Balance Confidence Scale (Tajali *et al.* 2017), the Falls Efficacy Scale International (Tajali *et al.* 2017) and the Berg Balance Scale (Dibble *et al.* 2013). No study reported corresponding sensitivity and specificity values together with the area under the receiver operating characteristic curve statistic value for these measures, but two different studies did report conflicting sensitivity values for the Berg Balance scale with one study reporting a high sensitivity value (greater than 80%) (Nilsagård *et al.* 2009) and another study reporting a contrasting sensitivity value of 32% (Prosperini *et al.* 2013). This conflicting value may be due to the variance in study population in the two cohorts with the latter study's participants representing a milder disease stage and a younger age profile than the former study (Nilsagård *et al.* 2009). The Berg Balance Scale should not be used to identify falls risk in Multiple Sclerosis until there is a stronger evidence base available demonstrating good discriminative ability and satisfactory clinical utility.

Our results are somewhat similar to a previous review by Gianni *et al* (Gianni *et al.* 2014), who found that measures such as the Berg Balance Scale and Timed Up and Go demonstrated poorer performance in fallers when compared to non-fallers. However, those authors meta-analysed data from both prospective and cross-sectional studies, thus diluting the validity of their pooled results. Gunn *et al* (2013b) looked at risk factors associated with falls in Multiple Sclerosis and found that balance impairment was associated with falling (pooled OR of 1.07, 95% CI 1.04 – 1.10). Like our findings, they also reported low measures of sensitivity in the balance measures used and concluded that the use of a balance measure alone is not appropriate when falls screening for people with Multiple Sclerosis. Given that studies from other populations (Paul *et al.* 2013; Barry *et al.* 2014) suggest that a balance measure alone may not have sufficient clinical utility to predict falls, we suggest those measures with significant differences on meta-analysis should be considered for evaluation in future studies in combination with other clinical variables.

There are a number of strengths associated with this systematic review. A robust methodological approach was employed to identify and select 33 unique studies relevant for inclusion which is higher than the previous reviews (Gunn *et al.* 2013b; Gianni *et al.* 2014). We utilised rigorous methods to select and carefully appraise appropriate studies from a variety of databases. However, the findings need to be interpreted in the context of our study limitations. We originally proposed to investigate only prospective cohort studies; however, a scoping search indicated that there were a limited number of papers reporting this reference standard. We therefore included data from cross sectional studies comparing balance scores in people who do and do not report falls in this systematic review and meta-analysed that data. There

was a lack of standardised conduct and reporting across the included studies with significant heterogeneity in the range of outcomes used. A strength is that we included all available studies, however a limitation is that some were of low methodological quality. The lack of a “cut off” or definition of “good” or “excellent” for the tools used meant that a clear rationale for excluding studies was not available and we did not use a sensitivity analysis to exclude certain studies from the meta-analyses.

A further limitation of this review is that we did not specify the fall definition or faller classification as part of our inclusion criteria. Our results demonstrate a wide variety of fall definitions and faller classifications and this, and lack of consideration of clinical heterogeneity due to Multiple Sclerosis type or level of disability weakens the findings from our meta-analyses. Only nine studies in this review used the gold standard of prospective falls recording with diaries as recommended by falls prevention networks such as the Prevention of Falls Network Europe (Lamb *et al.* 2005) and the International Multiple Sclerosis Falls Prevention Research Network (Coote *et al.* 2014). We used a broad range of search terms to try and find all suitable studies, but the large numbers returned in our initial results may have resulted in suitable studies being missed at the screening stage. We chose to exclude laboratory-based measures of balance such as posturography using force plate platforms due to the lack of clinical applicability. However, there is a growing body of evidence on their discriminative ability and clinical utility in people with Multiple Sclerosis (Prosperini and Pozzilli 2013) and in the use of inertial sensors and instrumented gait tests to detect balance impairments in this population (Spain *et al.* 2012; Greene *et al.* 2014).

In conclusion, it is not currently possible to recommend any clinical balance measure for assessing falls risk in Multiple Sclerosis. From the small number of prospective studies presented in this review, it is clear that we do not have enough information about the predictive validity of the current measures commonly used to recommend any specific one. Given the multifactorial nature of falls, balance measures alone may not have adequate falls prediction ability. Similar to research on falls risk in older people (Stevens and Phelan 2013), the use of quick screening questions rather than results of a lengthy assessment may more reliably identify those at risk, and further research should consider this direction.

Clinical Message

- Meta-analysis shows fallers perform significantly worse than non-fallers on commonly used measures such as the Berg Balance Scale and Timed Up and Go, but the discriminative ability of these clinical measures is poor.
- It is not possible to recommend any clinical balance measure for assessing falls risk in Multiple Sclerosis.

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Chapter 3:

Discriminative Ability and Clinical
Utility of the Timed Up and Go, TUG,
in Identifying Falls Risk in people with
Multiple Sclerosis; a Prospective
Cohort Study

Paper Status: published in Clinical Rehabilitation

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Susan Coote.

Authors' Contributions:

The author of this thesis (GQ) contributed to the paper as follows-

- Participated in study concept and design.
- Liaised with Chris McGuigan to aid participant recruitment.
- Conducted assessments of the TUG and TUG-Cognitive and all other components of data collection.
- Analysed the data using SPSS with guidance from Susan Coote and Rose Galvin.
- Wrote the paper and submitted for publication.

LC assisted with data collection and manuscript preparation. RG assisted with statistical analysis and manuscript preparation. CM participated in study concept and design and assisted with participant recruitment. SC participated in study concept and design and assisted with manuscript preparation. All authors read and approved the final manuscript.

Abstract:

Objective:

To investigate discriminative ability and clinical utility of the Timed Up and Go under single and dual task conditions between fallers and non-fallers in Multiple Sclerosis.

Design:

Prospective cohort study.

Setting:

Neurology service in a tertiary hospital.

Subjects:

Participants were 101 people with Multiple Sclerosis and Expanded Disability Status Score of 3-6.5. One participant withdrew after the baseline assessment, data were analysed for 100 participants.

Interventions:

No specific intervention.

Main Measures:

Timed Up and Go and Timed Up and Go Cognitive. Three-month prospective diaries recorded falls.

Results:

Mean age was 52.6 (SD 10.7) and 66 were female. Majority of participants had progressive MS (72) and 73 used a walking aid, 56 participants recorded 791 falls. The area under the receiver operating characteristic curve for Timed Up and Go and Timed Up and Go -Cognitive in distinguishing fallers (person with ≥ 1 fall) from non-fallers is 0.60 and 0.57 respectively, in distinguishing multiple fallers (≥ 2 falls) it is 0.46 and 0.43. A Timed Up and Go score of ≥ 9 seconds, has sensitivity of 0.82 and specificity of 0.34 to identify fallers, and sensitivity of 0.79 and specificity of 0.27 to identify multiple fallers. A Timed Up and Go-Cognitive score of ≥ 11 seconds has sensitivity of 0.77 and specificity of 0.30 to identify fallers and sensitivity of 0.71 and specificity of 0.26 to identify multiple fallers

Conclusion:

The Timed Up and Go and Timed Up and Go-Cognitive do not demonstrate sufficient clinical utility or discriminative ability for assessing falls risk in MS.

Key Words:

Multiple Sclerosis; Accidental Falls; Risk; Timed Up and Go

Introduction:

Multiple Sclerosis is a chronic progressive disease with a high incidence of falls (Nilsagård *et al.* 2015). Poor balance and cognition, progressive Multiple Sclerosis and mobility aid use are all risk factors associated with falling (Gunn *et al.* 2013). The consequences of falls are far reaching including serious injury, fear of falls and associated activity curtailment, with increased healthcare utilization that contributes to a high socio-economic cost (Peterson *et al.* 2008; Larkin *et al.* 2015). Reliable screening tools are essential to allow early identification of people with Multiple Sclerosis who are at risk of falling and initiate more timely and appropriate falls prevention interventions. A recent systematic review (Quinn *et al.* 2017) and meta-analysis found that no clinical balance measure currently in use has sufficient evidence for its suitability in assessing falls risk in Multiple Sclerosis and noted poor methodological standards of included studies.

One of the most common measures utilised to assess dynamic balance and functional mobility in Multiple Sclerosis research is the Timed Up and Go and meta-analysis found significant differences between fallers and non-fallers (Quinn *et al.* 2017) suggesting further investigation of this measure as a predictor of falls is warranted. The Timed Up and Go has been recommended as a screening test for falls risk by the American Geriatrics Society/British Society of Gerontology Guidelines (2011) and has been shown to have good validity (Sebastião *et al.* 2016) and reliability (Nilsagård *et al.* 2007) in Multiple Sclerosis populations. The Timed Up and Go-Cognitive comprises the same mobility task with an added cognitive task such as counting backwards or verbal fluency and provides a simple method of assessing the dual task

cost of walking which has been shown to be associated with falls risk (Wajda *et al.* 2013) in people with Multiple Sclerosis. Both the Timed up and Go and Timed up and Go-Cognitive have been recommended for use in Multiple Sclerosis research and clinical practice by the American Physical Therapy Association Evidence Database to Guide Effectiveness Task Force (Potter *et al.* 2014).

Retrospective studies investigating falls risk assessment in Multiple Sclerosis using the Timed Up and Go have reported conflicting findings with one study not finding any significant difference between fallers (faller classification not specified) and non-fallers (Cattaneo *et al.* 2006) while a more recent study (Kalron *et al.* 2017) with a larger sample size demonstrated a significant difference between non-fallers and multiple fallers (person with 2 or more falls). The only two prospective studies that have reported on the discriminative ability (ability to distinguish between fallers and non-fallers) of the Timed Up and Go found it has poor discriminative ability to identify future fallers with an area under the receiving operating curve value of less than 0.7 (Dibble *et al.* 2013; Tajali *et al.* 2017) with no study reporting the measure as having both good clinical utility (assessed using the summary estimates of sensitivity and specificity) and good discriminative ability.

This prospective cohort study aims to investigate both the discriminative ability and clinical utility of the Timed Up and Go under single and dual task conditions among people with Multiple Sclerosis with mixed condition subtypes using prospectively collected falls data.

Methods:*Study design*

This was a prospective cohort study with prospectively collected falls status using diaries. The STROBE (STrengthening The Reporting of OBservational studies in Epidemiology) Statement guideline (Von Elm *et al.* 2007) was adhered to in the conduct and reporting of the study. The study was approved by the University of Limerick Ethics Committee and the St. Vincent's Healthcare Group Ethics and Medical Research Committee.

Recruitment and Eligibility

Consecutive patients attending the MS clinic at St Vincent's University Hospital Dublin were invited to participate in the study if they met the following inclusion criteria: (1) A neurologist confirmed diagnosis of MS, (2) an Expanded Disability Status Score of between 3 and 6.5 (Kurtzke 1983) indicating that they had some walking limitations but were still able to ambulate independently (with or without a mobility aid), (3) adequate cognitive function to participate in the assessment and fill out falls diaries for the three-month study period. Participants under 18 years, pregnant woman or individuals unable to provide informed consent were excluded from the study. There were no other exclusion criteria and participants could have other conditions that directly or indirectly affected walking ability and may have been on symptomatic treatment that affected their mobility. Recruitment and participant assessment was carried out between November 2014 and March 2016 with the final falls diaries collected in June 2016.

Measures/Outcomes

The primary outcome was falls incidence as reported using prospective falls diaries for a three-month period. A fall was defined as ‘an unexpected event in which you come to rest on the ground, floor, or lower level’ (Lamb *et al.* 2005). The participants were provided with stamped self-addressed envelopes and falls diaries to be returned monthly. Those not returning their diaries were contacted by the researcher to remind them or to collect the data for that month by phone. Participants also had the option of a text or e-mail reminder to be sent fortnightly to optimise falls reporting. As there are a variety of classifications for faller status currently utilized in the literature (Matsuda *et al.* 2011) , we analysed our data using two faller classifications; those who had 1 or more falls and those with multiple falls (2 or more) in the three month period.

Data collected routinely at the clinic was incorporated into the data set for the study and included the Expanded Disability Status Score (level of disability), age, time since diagnosis, self-reported falls in the last 3 months, type of Multiple Sclerosis and walking aid(s) used. Consenting participants then completed the Timed Up and Go. The measures were performed in the same standardised order for every participant and participants were advised to walk at a fast but safe speed while in their usual footwear and using their usual mobility device (if applicable). This instruction was chosen as it has been previously used in studies examining the TUG with people with MS (Gijbels *et al.* 2010). It is acknowledged that instructions for the TUG have varied in the literature (Barry *et al.* 2014) but previous exploration of walking assessment in people with MS have recommended participants are instructed to walk fast in order to maximise effort and better assess motor fatigue (Goldman *et al.* 2008). The participant was seated in a standard height chair with their back against the chair and was then

instructed to stand up, walk 3 metres to a specific mark on the ground, turn around, and walk back and sit in the chair again. Timing began when the participant started to rise from the chair and ceased when he/she was seated in the chair after walking back. The participant had one practice trial and then three recorded trials, with a mean value of the three walks used for statistical analysis. The participant then did the Timed Up and Go under dual task conditions with an added cognitive task of counting backwards in multiples of three. The starting number chosen by the research assistant was a randomly selected number between 20 and 100. The Timed Up and Go-Cognitive was assessed in the same standardised manner as the TUG.

Statistical Analysis

Descriptive statistics were generated for age, gender, disease duration, Multiple Sclerosis type and Expanded Disability Status Score. Timed Up and Go data was tested for normality using the Kolmogorov-Smirnov test and depending on distribution either independent sample T tests or Mann Whitney tests were used to determine the differences between fallers and non-fallers. Discrimination is the ability of a measure to differentiate between individuals with and without falls and is quantified using the area under the receiver operating characteristic curve statistic. Receiver operating curve analysis was carried out to determine this value and the optimal sensitivity and specificity values for the Timed Up and Go and Timed Up and Go-Cognitive. The area under the receiver operating characteristic curve statistic measures the average true positive rate (predicted falls that actually occurred) over all false positive rates (predicted falls that did not actually occur). It can have any value between 0 and 1 with a value of 0.5 representing chance, values between 0.7 and 0.9 representing moderate discrimination and a value of 1 representing perfect discrimination (Moons *et al.*

2015). The larger the area under the receiver operating characteristic curve statistic value the greater the discriminative ability of the measure in question (Hanley and McNeil 1982). In terms of measuring clinical utility, the sensitivity and specificity of the Timed Up and Go and Timed Up and Go-Cognitive were calculated. Balance screening tools with high sensitivity ($\geq 80\%$) are preferable to safely ‘rule-out’ those at low risk of a subsequent fall (as opposed to diagnostic tools that generally demonstrate high specificity) (Riddle and Stratford 1999).

Positive predictive values and likelihood ratios were also calculated. A positive predictive value is the proportion of individuals with test results above or equal to the cut-off point who were correctly classified as fallers. The specific cut offs used were chosen to maximise the sensitivity and specificity values as previous cut off values have not been recommended in this population. A negative predictive value is the proportion of individuals with scores below the cut-off point who were correctly classified as non-fallers. The likelihood ratio summarizes how many times more a person who experiences falls has results on the Timed Up and Go or Timed Up and Go-Cognitive worse than or equal to the cut-off score. A positive likelihood ratio of greater than 1 indicates the test result is associated with the disease or in this instance with faller status. A negative likelihood ratio less than 1 indicates that the result is associated with absence of the disease or in this instance being a non-faller (Jaeschke *et al.* 1994).

As this is not an intervention trial there was no formal study size calculation, the sample size of 100 was chosen based on previous research in this field (Prosperini *et*

al. 2013) and was considered a feasible and realistic recruitment target. All analyses were performed using SPSS software, version 22. The level of significance was set as $p < 0.05$.

Results:

The sample included 101 people with Multiple Sclerosis (67 female), one participant withdrew after the baseline assessment, so data was analysed for a total of 100 participants with three months of falls diaries. Baseline details for fallers (person with 1 or more falls) and non-fallers (0 falls) are reported in Table 3.1. There was no significant difference in the Timed Up and Go or Timed Up and Go-Cognitive scores between fallers and non-fallers ($p > 0.05$). If examining the baseline differences between multiple fallers (person with 2 or more falls) and non-fallers, there was a significant difference in age ($p = 0.003$) and disease duration ($p = 0.007$) with the multiple fallers being younger with a shorter disease duration.

Table 3.1: Comparison of demographic information and clinical characteristics of fallers (≥ 1 fall) and non-fallers (0 falls) with Multiple Sclerosis.

<i>Characteristic</i>	<i>All Participants (n=100)</i>	<i>Fallers (n=56)</i>	<i>Non-Fallers (n=44)</i>	<i>p Value</i>
<i>Age (years); mean (SD) [range]</i>	52.6 (10.78) [29-78]	51.61 (11.3) [29-78]	53.86 (10.1) [31-71]	0.30 ^a
<i>Gender; n (%)</i>				
<i>Male</i>	34	22 (39.3)	12 (27.2)	0.21 ^b
<i>Female</i>	66	34 (60.7)	32 (72.7)	
<i>MS Classification; n (%)</i>				
<i>Primary</i>				0.81 ^c
<i>Progressive</i>	19	10 (17.9)	9 (20.5)	
<i>Secondary</i>				
<i>Progressive</i>	53	31 (55.4)	22 (50)	
<i>Relapsing- Remitting</i>	24	13 (23.2)	11 (25)	
<i>Benign</i>	2	0 (0)	2 (4.5)	
<i>Unknown</i>	2	2 (3.6)	0 (0)	
<i>Use of a Walking Aid; n (%)</i>				
<i>Yes</i>	73	44 (78.6)	29 (65.9)	0.16 ^b
<i>No</i>	27	12 (21.4)	15 (34.1)	
<i>EDSS; median [IQR]</i>	6 (2)	6 (1.5)	5.5 (2)	0.24 ^d
<i>Time Since Diagnosis (years); median [IQR]</i>	14 [13.75]	11 [15.5]	14.25 [10.4]	0.08 ^d
<i>Fall in the Past 3 Months (self report); n (%)</i>				
<i>Yes</i>	50	35 (62.5)	15 (34.1)	0.01 ^b
<i>No</i>	50	21 (37.5)	29 (65.9)	
<i>TUG score (secs); median [IQR]</i>	11.56 [6]	12.0 [7.7]	11.2 [5.2]	0.09 ^d
<i>TUG C score (secs); median [IQR]</i>	13.35 [6.8]	13.5 [10.9]	13.0 [5]	0.22 ^d

SD: Standard Deviation, MS: Multiple Sclerosis, EDSS: Expanded Disability Status Scale, IQR: Interquartile Range, ^a*p* value from independent samples t-test, ^b*p* value from chi square test for independence (continuity correction), ^c*p* value from Fisher's exact test, ^d*p* value from Mann-Whitney U test.

The area under the receiver operating characteristic curve statistic values with optimal sensitivity and specificity values, the positive predictive value and negative predictive value and positive likelihood ratio and negative likelihood ratio are all reported in Table 3.2 below.

Table 3.2: The AUC, sensitivity and specificity, predictive values and likelihood ratios for the TUG and TUG -Cognitive.

Faller Classification	AUC (95% CI)	Cut off, secs	Sensitivity (95% CI)	Specificity (95% CI)	PV+ (95% CI)	PV- (95% CI)	LR+ (95% CI)	LR- (95% CI)
1 or more falls	TUG 0.60 (0.5-0.7)	9	82.1% (69.6-91.1)	34.1% (20.5-49.9)	61.3% (53.4-67.0)	60.0% (42.8-75.1)	1.3 (1.0-1.6)	0.5 (0.3-1.1)
	TUG C 0.57 (0.5-0.7)	11	76.8% (63.6-87.0)	29.6% (16.8-45.2)	58.1% (52.2-63.8)	50.0% (34.1-65.9)	1.1 (0.9-1.4)	0.8 (0.4-1.5)
2 or more falls	TUG 0.46 (0.4-0.6)	9	79.4% (62.1-91.3)	27.3% (17.0-39.6)	36% (31.0-41.4)	72% (54.4-84.7)	1.09 (0.9-1.4)	0.8 (0.4-1.6)
	TUG C 0.43 (0.3-0.6)	11	70.6% (52.5-84.9)	25.8% (15.8-38.0)	32.9% (46.7-76.7)	63.0% (31.3-51.3)	1 (0.7-1.2)	1.1 (0.6-2.2)

AUC: Area under the receiving operating curve statistic, TUG: Timed Up and Go, TUG C: Timed Up and Go Cognitive, PV+: Positive Predictive Value, PV-: Negative Predictive Value, LR+: Positive Likelihood ratio, LR-: Negative Likelihood ratio

The 2 x 2 table used to calculate these values is shown in Table 3.3 below.

Table 3.3: 2 x 2 Table for Timed Up and Go with a cut point of 9 seconds and a faller classification of ≥ 1 fall.

Test (Timed Up and Go)	Faller (condition present)	N =	Non-Faller (condition absent)	N =	Total
Positive	True positive	46	False positive	29	75
Negative	False Negative	10	True Negative	15	25
Total		56		44	100

The receiver operating characteristic curve is shown in Figure 3.1 for fallers and in Figure 3.2 for multiple fallers. The area under the receiver operating characteristic curve statistic for the Timed Up and Go and Timed Up and Go-Cognitive in distinguishing fallers from non-fallers is 0.60 and 0.57 respectively and is 0.46 and 0.43 for multiple fallers.

Figure 3.1: Receiver Operating Curve analysis for Timed Up and Go (TUG) and Timed up and Go -Cognitive (TUG COG) in predicting fallers (≥ 1 fall) in Multiple Sclerosis

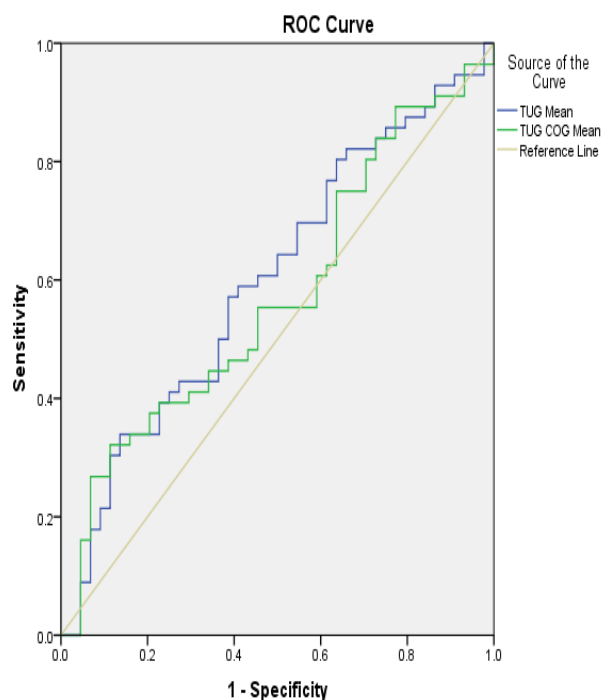
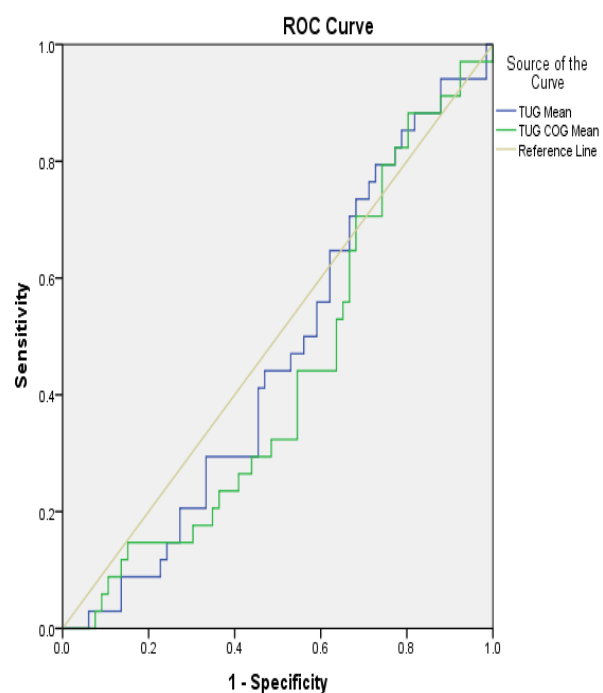


Figure 3.2: Receiver Operating Curve analysis for Timed Up and Go (TUG) and Timed Up and Go-Cognitive (TUG COG) in predicting multiple fallers (≥ 2 falls) in Multiple Sclerosis



Discussion:

This prospective cohort study is the first to report both the discriminative ability and the clinical utility of the Timed Up and Go and Timed Up and Go-Cognitive for assessing falls risk among people with Multiple Sclerosis using prospective falls diaries. The findings demonstrate that both the Timed Up and Go and Timed Up and Go-Cognitive scores are not significantly different between fallers and non-fallers and the discriminative ability of these measures is poor with an area under the receiving operating curve value of 0.60 and 0.57 respectively. When explored using the faller classification of 2 or more falls the discriminative ability is reduced with an area under the receiving operating curve value of 0.46 and 0.43 for the Timed Up and Go and Timed Up and Go-Cognitive. Neither of these measures demonstrated a prediction accuracy high enough (greater than 0.7) to warrant their use in isolation for assessing falls risk in this progressive Multiple Sclerosis cohort.

Our finding that the Timed Up and Go and Timed Up and Go-Cognitive scores are not significantly different between fallers and non-fallers, for both faller and multiple faller classifications, is similar to a previous prospective study examining the utility and predictive validity of specific clinical measures for falls risk in Multiple Sclerosis (Dibble *et al.* 2013) but differs from findings from a recent systematic review and meta-analysis of studies using retrospective falls reporting (Quinn *et al.* 2017). Other studies did not report clinical utility in the form of sensitivity and specificity values or discriminative ability (Sosnoff *et al.* 2011; Kalron *et al.* 2017). To properly examine the discriminative ability of a measure and its validity in identifying future risk of falls prospective study designs should be employed using appropriate indices of

discrimination and clinical utility. An area under the receiving operating curve value of greater than 0.7 is necessary to be of moderate discrimination and previous prospective studies in Multiple Sclerosis have reported similarly low discrimination values for the Timed Up and Go of 0.66 (Dibble *et al.* 2013) and 0.65 (Tajali *et al.* 2017). The latter study above had a younger cohort with primarily relapsing remitting Multiple Sclerosis in comparison to our study sample that had mainly progressive Multiple Sclerosis and a median disease duration of 14 years (IRQ 13.75). This poor discriminative ability is evident in research on other neurological populations also with an area under the receiving operating curve value of 0.58 reported in a large study on falls risk in older people (Kojima *et al.* 2015) and an area under the receiving operating curve value of 0.65 for people with Parkinson's disease (Kerr *et al.* 2010).

In other neurological populations the evidence for clinical utility of the Timed Up and Go is conflicting. The measure has demonstrated very high sensitivity in Parkinson's disease (Dibble and Lange 2006) but much lower sensitivity in people post stroke (Andersson *et al.* 2006) and in community dwelling elderly a recent systematic review and meta-analysis (Barry *et al.* 2014) found the measure had an overall sensitivity of 31% and specificity of 74% at a cut-point of ≥ 13.5 seconds and that it is not a significant predictor of falls with an odds ratio of 1.01. No prospective study in Multiple Sclerosis has reported sensitivity or specificity values for the Timed Up and Go and only one Multiple Sclerosis study has reported sensitivity values for the Timed Up and Go-Cognitive (Nilsagård *et al.* 2009) which was similar to our values reported here. However, that study demonstrated a higher specificity and a higher positive predictive value in comparison to our results when used with a cut off value of 13.6 seconds. The low specificity value of 29% for the Timed Up and Go-Cognitive from

our data may mean that some people would end up being classed as falls risk incorrectly and would be referred for in demand resources and falls prevention services that they may not actually need. Regarding clinical utility, in the form of sensitivity and specificity values, the current literature suggests the Timed Up and Go and Timed Up and Go-Cognitive are not reliable enough to use as a stand-alone measure of falls risk.

Interestingly, no other studies of people with Multiple Sclerosis reported predictive values or likelihood ratios for the Timed Up and Go which is of concern when it has been argued that likelihood ratios are more useful clinically when discussing diagnostic accuracy. The further likelihood ratios are from 1 the stronger the evidence for the presence or absence of disease or in this instance of being a faller or non-faller (Deeks and Altman 2004). The only other prospective study that reports predictive values and likelihood ratios for the Timed Up and Go-Cognitive in relation to falls risk in Multiple Sclerosis had a slightly higher positive predictive value and positive likelihood ratio (Nilsagård *et al.* 2009) than our findings, but was well outside the range of above 10 or below 0.1 that is considered as strong evidence for ruling in or out conditions (Jaeschke *et al.* 2002). These poor likelihood ratio values demonstrated in Multiple Sclerosis are similar to that seen for the Timed Up and Go and Timed Up and Go-Cognitive in Parkinson's disease (Dibble and Lange 2006) and suggest that the measure has poor diagnostic accuracy or in this context poor predictive ability for determining faller status.

If the Timed Up and Go is used to measure falls risk, it may need to be more objectively quantified using body worn sensors as has been shown to increase the accuracy of falls risk detection in a small prospective study of people with Parkinson's disease (Greene *et al.* 2018). When trying to quantify falls risk, various dimensions of mobility across a variety of contexts may need to be investigated and a recent study found self-report measures demonstrated stronger reliability than performance based measures such as the Timed Up and Go (Tajali *et al.* 2017). A measure such as the Timed Up and Go that only examines one aspect of performance in the form of speed may be too crude to fully quantify falls risk and ideally should be combined with other variables to improve its predictive validity. Furthermore, recent research has shown that the activity at the time of falling and influencing factors such as individual symptoms and task demands are important considerations when monitoring falls risk (Carling *et al.* 2018) and perhaps assessment in the home during a more real life situation may be more useful than a clinic based tool.

A limitation of this study is that recruitment rate and reasons for non-participation cannot be clearly identified. As recruitment occurred in a busy outpatient neurology clinic the number of potentially eligible participants and the number of participants deemed eligible is unknown as this initial screening was done by the treating physician and participants were only introduced to the principal investigator once deemed appropriate. This may explain why the study sample consists of such a progressive cohort as the treating physician may only have considered falls risk in the more physically impaired clinic attendees. As the median Expanded Disability Status Score was 6 this indicates that some participants were using bilateral support for walking and this alters the balance requirements of the Timed Up and Go and limits the

applicability of the study findings to a less disabled Multiple Sclerosis cohort. A further limitation was lack of a formal study size calculation, the sample size of 100 was chosen based on previous research in this field (Prosperini *et al.* 2013) and was considered a feasible and realistic recruitment target. The lack of a measure for the dual task of cognition in conjunction with the dual task of mobility is also a limitation of this study. Recent studies on dual task ability and cognitive motor interference recommend that both the cognitive and motor aspects be assessed (Plummer and Eskes 2015).

There are many strengths associated with this study such as the large sample size and the robust methodology including clear reporting of both discrimination and clinical utility. The predominantly progressive cohort may be a limitation in that these results cannot be applied to people with Multiple Sclerosis with less impaired mobility. However, as longer disease duration and more progressive disease are strongly associated with an increased falls risk (Gunn *et al.* 2013; Giannì *et al.* 2014) this population warrants investigation. A strength is the use of prospective diaries as opposed to retrospective recall, but a limitation is the relatively short falls monitoring period as many studies in the elderly would include follow up periods of 6 months to 2 years (Ersoy *et al.* 2009; Ward *et al.* 2015). While the accuracy of data provided by falls diaries may be questionable, this was minimized by using text reminders in conjunction with the falls diaries and telephone follow up at the end of the monthly reporting period to clarify any missing information.

In conclusion, the Timed Up and Go and Timed up and Go-Cognitive do not demonstrate sufficient clinical utility or discriminative ability for assessing falls risk in progressive Multiple Sclerosis and should not be used in isolation as a falls screening tool in this population. The high area under the receiving operating curve value associated with self-report measures (Tajali *et al.* 2017) must also be taken into account and future research should consider combining subjective variables with an objective performance-based measure to obtain a more reliable and valid falls screening tool.

Clinical Message:

- The Timed up and Go does not demonstrate sufficient clinical utility or discriminative ability for assessing falls risk in people with Multiple Sclerosis and should not be used in isolation as a falls screening tool.
- Combining self-report variables with a performance-based measure may result in a more reliable screening tool.

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Chapter 4:

An Exploration of Falls and Dual Tasking; a prospective cohort study of people with Multiple Sclerosis

*Paper Status: accepted for a special edition of Topics in Geriatric
Rehabilitation*

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Rose Galvin, Susan Coote.*

Authors' Contributions:

The author of this thesis (GQ) contributed to the paper as follows-

- Participated in study concept and design.
- Liaised with Chris McGuigan to aid participant recruitment.
- Assessments of single task and dual task activity and data collection.
- Analysed the data using SPSS with guidance from Susan Coote and Rose Galvin.
- Wrote the paper and submitted for publication.

LC assisted with data collection and manuscript preparation. NOM assisted with manuscript preparation and data analysis. RG assisted with statistical analysis and manuscript preparation. CM participated in study concept and design and assisted with participant recruitment. SC participated in study concept and design and assisted with manuscript preparation. All authors read and approved the final manuscript.

Abstract:

Objective: To explore the relationship between dual task cost (DTC) and falls in people with Multiple Sclerosis.

Methods: 100 participants completed a falls screening questionnaire, Timed Up and Go (TUG), and TUG Cognitive (TUG-C) at baseline. DTC was the percentage change in performance between TUG and TUG-C. Falls were recorded prospectively for three months.

Results: DTC was not associated with increased risk of falls ($p=0.90$, odds ratio=1.00). Answering yes to a question about problems doing two things at once increased likelihood of falls (risk ratio=2.07).

Conclusion: A single question asking about dual tasking may be a useful screen for falls risk assessment.

Key Words: Multiple Sclerosis, Accidental Falls, Cognitive-Motor Interference, Dual-Task Cost.

Introduction:

Accidental falls are well known to be prevalent in older people; however, people aging with Multiple Sclerosis (MS) experience a rate of accidental falls that far exceeds that of healthy populations over 65 years of age. In any three month period, 50% of people with MS sustain a fall (Nilsagård *et al.* 2015). When examining falls specifically among middle aged and older adults with MS, 64% of the study sample reported at least 2 falls each year (Peterson *et al.* 2008) and factors associated with an increased falls risk in people aged 45 to 90 with MS include problems with balance or mobility and poor concentration or forgetfulness (Finlayson *et al.* 2006). The serious consequences of falls such as physical injury, increased care needs, and further physical deconditioning as a result of activity limitation secondary to fear of falling are far reaching with a high socio-economic associated cost (Peterson *et al.* 2009; Cameron *et al.* 2011). People with MS are commonly diagnosed in their thirties and thus may be living with the condition for 40-50 years as MS does not affect life expectancy unless disability is severe (Weinshenker *et al.* 1989; Ragonese *et al.* 2008). People aging with MS will have to endure normal age-related changes in their health as well as having to cope with MS related disability and disease progression (Finlayson 2002). Indeed, many symptoms of the natural ageing process such as decreased muscle strength, sensory and visual impairment, problems with balance, vision and cognition are all overlapping symptoms in MS (Stern *et al.* 2010) and mean that relatively “young” people with MS will present with problems similar to older adults.

Two of the most common symptoms of MS include motor dysfunction and a decline in cognitive ability (McDonald and Compston 2006). Difficulty walking has been reported as a significant symptom by up to 67% (Wu *et al.* 2007) of people with MS and even in the early stages of the disease, significantly altered gait patterns are evident in comparison to their healthy peers (Comber *et al.* 2017). Notably, middle aged cohorts (Hayes *et al.* 2017) have demonstrated reduced walking speeds similar to that of a healthy sample of 70 – 80 year olds (Casanova *et al.* 2010). Similarly prevalence of cognitive impairment has been reported to be present in up to 70% of people with MS (Rao *et al.* 1991), presenting early in the disease course and deteriorating over time (Langdon 2011). Limitations in mobility and cognitive functioning are both associated with falls in older people (Rubenstein 2006; Eriksson *et al.* 2008) and similarly the association of both walking limitations and cognitive factors with falls is confirmed in a recent systematic review of falls risk factors in MS (Gunn *et al.* 2013b). Among middle aged and older adults with MS interviewed about their falls experience, expected causes of falls such as balance and lower limb impairment were reported in 41% and 31% of cases, but interestingly cognitive factors were reported as a cause of falls in 17% of cases (Peterson *et al.* 2013).

These two factors of impaired cognition and impaired mobility together underlie the principle of cognitive motor interference (CMI) which is common in MS (Leone *et al.* 2015) and refers to the decline in performance of cognitive and/or motor tasks when they are performed simultaneously (dual-task), relative to the performance of each task individually (Plummer *et al.* 2013). The deterioration in performance associated with CMI is expressed as dual-task cost (DTC) (Wajda and Sosnoff 2015) and has been shown to be associated with falls in older people (Beauchet *et al.* 2008). However,

there is a scarcity of studies looking at the association of DTC and falls risk using prospective falls recording in people with MS. Previous research demonstrated conflicting results with one study reporting DTC is not related to falls status (Gunn *et al.* 2013a), while another more recent study found DTC is associated with an increased risk of recurrent falls in a 6 month period (OR = 1.23, CI = 1.02,4.45.) (Etemadi 2016). In studies of older people simply asking about fear of falls and their confidence in doing certain activities have been shown to be associated with falls risk (Howland *et al.* 1993; Myers *et al.* 1996) but their perceived ability to do two things at once in relation to falls risk has not been fully explored. Similarly, in MS, self-report problems with dual tasking and its potential association with falls risk has not been examined. In a recent review examining patterns of CMI post stroke a categorisation framework that identifies nine possible patterns of CMI during a cognitive-motor dual-task was presented (Plummer *et al.* 2013). The patterns of CMI discussed include no interference, cognitive-related motor interference, mutual interference and mutual facilitation among others. No research to date has examined the patterns of cognitive motor interference (CMI) in people ageing with MS and whether the use of any specific pattern is protective or predictive of falls.

Given the current shortage of prospective cohort studies examining DTC and CMI and their potential association with falls risk in the older MS population, the primary objective of this study was to explore the extent of CMI in fallers and non-fallers and investigate the difference between them by measuring it objectively as DTC percentage and subjectively as a yes/no question asking about difficulty doing two things at once. We further aimed to investigate the ability of objective and subjective measures of DTC and CMI to predict falls status using odds ratio and risk ratio.

Finally, we aimed to describe the different CMI patterns used among people with MS and examine their association with fall status.

Methods:

Design

This was a prospective cohort study and as this is an observational study we followed the STROBE (STrengthening The Reporting of OBservational studies in Epidemiology) Statement guideline (von Elm *et al.* 2007). The study was approved by the University of Limerick Ethics Committee and the St. Vincent's Healthcare Group Ethics and Medical Research Committee.

Recruitment and Eligibility

Consecutive patients attending a tertiary referral MS clinic at St Vincent's University Hospital Dublin were invited to participate in the study if they met the following inclusion criteria: (1) a neurologist confirmed diagnosis of MS as per 2010 McDonald Criteria (Polman *et al.* 2011), (2) an Expanded Disability Status Score (EDSS) of between 3 and 6.5 (Kurtzke 1983) indicating that they had some walking limitations but were still able to ambulate independently (with or without a mobility aid), (3) adequate cognitive function to participate in the assessment and fill out falls diaries for the three-month study period. Participants under 18 years, pregnant woman or individuals unable to provide informed consent were excluded from the study.

Recruitment and participant assessment was carried out between November 2014 and March 2016 with the final falls diaries collected in June 2016.

Baseline Measures

Demographic information, MS classification subtype, EDSS score and disease duration were recorded from the medical records during the baseline assessment. Consenting participants then completed a falls screening questionnaire which included yes/no questions about fear of falls, use of a mobility aid, history of falls in the past three months, and problems doing two things at once among others. The questionnaire items were based on a review of the literature on factors associated with and predictive of falls in MS. Participants then completed the objective measures, the Timed Up and Go (TUG), under single and dual task conditions. The TUG has been shown to be a valid measure of functional mobility in MS patients (Sebastião *et al.* 2016) with good construct validity when assessing walking and balance performance among people with MS (Kalron *et al.* 2017). Previous research found that more than 80% of falls in the MS population occurred during transfers, while 60% occurred during walking (Matsuda *et al.* 2011). The TUG incorporates both types of mobility task, so its face validity appears good in relation to determining falls status and it has been previously used to assess dual task ability in people with MS (Ciol *et al.* 2017).

The TUG-Cognitive (TUG-C) was performed after the TUG and consisted of the participant completing the same mobility test, while simultaneously performing a cognitive task. For this study, the cognitive task consisted of serial subtraction in multiples of three from a randomly chosen number between 20 and 100. Serial

subtraction was selected as it has a stable cognitive load throughout the duration of the test (Yogev *et al.* 2008). Dual-tasking ability was also measured subjectively as individuals were asked about their self-perceived dual-tasking ability as part of the falls screening questionnaire: ‘Do you have problems doing two things at once: yes, or no?’. The measures were performed in the same standardised order for every participant and participants were advised to walk as quickly and safely as possible while in their usual footwear and using their usual mobility device (if applicable). The participant was seated in a standard height chair with their back against the chair and was then instructed to stand up, walk 3 metres to a specific mark on the ground, turn around, and walk back and sit in the chair again. Timing began when the participant started to rise from the chair and ceased when he/she was seated in the chair after walking back. The participant had one practice trial and then three recorded trials, with a mean value of the three walks used for statistical analysis.

Dual Task Cost (DTC)

DTC was calculated using the previously published equation, where ST = single task and DT = dual task (Kirkland *et al.* 2015) :

$$DTC = \frac{ST - (DT)}{ST} \times 100$$

Therefore, for this study, DTC was calculated and expressed as a percentage, with a larger percentage change value indicating a worse performance, with the following equation:

$$DTC = \frac{(TUG) - (TUG - C)}{TUG} \times 100$$

To determine the patterns of CMI three assessors (two physiotherapists with 20 and 3 years of experience respectively, and a final year physiotherapy student) observed the pattern of interference during the TUG-C of the first 12 participants. Following this, the assessors met to agree on categories, with six different patterns identified. The pattern of the remaining participants was recorded based on their use of one of the following six patterns:

Pattern 1: no changes in gait, numbers correct

Pattern 2: no changes in gait, numbers incorrect

Pattern 3: changes in gait, numbers incorrect

Pattern 4: stop, think and say number, take step

Pattern 5: synchronise step and think

Pattern 6: changes in gait, numbers correct

Falls

Falls incidence was calculated using prospective falls diaries for a three-month period, as recommended by the International MS Falls Prevention Research Network (IMSFPRN) (Coote *et al.* 2014) where participants recorded if they had a fall and the number of falls per day. A fall was defined as ‘an unexpected event in which you come to rest on the ground, floor, or lower level’ (Lamb *et al.* 2005). The participants were provided with stamped self-addressed envelopes and falls diaries to be returned monthly. Those not returning their diaries were contacted by the researcher to remind them or to collect the data for that month by phone. Participants also had the option of

a text or e-mail reminder to be sent fortnightly to optimise falls reporting. Consistent with other studies of this type a faller was classified as a person with two or more falls (Gunn *et al.* 2013a; Etemadi 2016).

Statistical Analysis

All data collected was coded and inputted into an Excel spreadsheet and then analysed using SPSS (Version 22). Normality of distribution was assessed using the Kolmogorov-Smirnov test. Descriptive statistics and t-tests or Mann-Whitney U tests, as appropriate, were used to compare demographic characteristics between groups at baseline and to compare outcome measures post assessment. Chi square tests were used for categorical variables. All data was presented as mean (standard deviation), median (interquartile range) or proportion accordingly. The relationship between objective measurement of DTC and fall status, was assessed using binary logistic regression to have a comparative methodology to previous studies on this topic (Gunn *et al.* 2013a; Etemadi 2016; Tajali *et al.* 2017). Chi square test was used to assess if self-reported problems with dual-tasking and pattern of CMI were different between the groups based on falls status. Risk ratio were calculated for subjective problems with dual tasking and for the various patterns of CMI. Missing data were excluded on analysis-by-analysis basis. The significance level for all statistics was set at $p \leq 0.05$.

Results:*Participant Characteristics:*

101 participants were recruited for this study, with falls data collected for 100 individuals. One participant withdrew from the study after the baseline assessment as they felt uncomfortable filling out the monthly falls diaries. A total of 791 falls were reported by 56 participants over the three-month reporting period with 34 of these individuals having 2 or more falls and meeting our criteria for faller classification. There was a diary return rate of 99.7%. In the faller group the number of falls ranged from 2 to 164 per faller with a mean number of 22.6 (SD 45.4) falls. Demographic information and clinical characteristics of the recruited participants are displayed in Table 4.1.

Table 4.1: Comparison of demographic information and clinical characteristics of fallers and non-fallers with Multiple Sclerosis.

<i>Characteristic</i>	<i>All Participants (n=100)</i>	<i>Fallers (n=34)</i>	<i>Non-Fallers (n=66)</i>	<i>p Value</i>
<i>Age (years); mean (SD) [range]</i>	52.6 (10.78) [29-78]	48.15 (10.49) [29-78]	54.89 (10.26) [31-71]	0.003 ^a
<i>Gender; n (%)</i>				
<i>Male</i>	34	15 (44.1)	19 (28.8)	0.13 ^b
<i>Female</i>	66	19 (55.9)	47 (71.2)	
<i>MS Classification; n (%)</i>				
<i>Primary</i>	19	6 (17.6)	13 (19.7)	0.77 ^c
<i>Progressive</i>				
<i>Secondary</i>	53	18 (52.9)	35 (53)	
<i>Progressive</i>				
<i>Relapsing- Remitting</i>	24	10 (29.4)	14 (21.2)	
<i>Benign</i>	2	0 (0)	2 (3)	
<i>Unknown</i>	2	0 (0)	2 (3)	
<i>Use of a Walking Aid; n (%)</i>				
<i>Yes</i>	73	24 (70.6)	49 (74.2)	0.697 ^b
<i>No</i>	27	10 (29.4)	17 (25.8)	
<i>EDSS; median [IQR]</i>	6 (2)	5.5 (1.8)	6 (2.5)	0.134 ^d
<i>Time Since Diagnosis (years); median [IQR]</i>	14 [13.75]	9 [10.25]	15 [12.25]	0.007 ^d
<i>Fall in the Past 3 Months (self- report at baseline); n (%)</i>				
<i>Yes</i>	50	26 (76.5)	24 (36.4)	<0.001 ^b
<i>No</i>	50	8 (23.5)	42 (63.6)	

SD: Standard Deviation, MS: Multiple Sclerosis, EDSS: Expanded Disability Status Scale,
 IQR: Interquartile Range, ^a*p* value from independent samples t-test, ^b*p* value from chi square test,
^c*p* value from Fisher's exact test, ^d*p* value from Mann-Whitney U test

Primary Outcome - DTC:

Objective measure of DTC (percentage change between the TUG and TUG-C)-

For the whole cohort of N=100, the median DTC was -13.19, IQR 21.60 (thus a 13% deterioration under dual task conditions as measured by the TUG and TUG-C). The range in DTC was from -169.30 to 12.42, indicating that some participants improved under dual task conditions and had a faster TUG-C than their TUG time (14

participants in total). The majority of participants, 86%, showed deterioration in mobility performance under dual task conditions with 46% of the total group demonstrating a change in DTC of greater than 15%, of whom 32.6% were fallers. No significant difference was found between the DTC of fallers and non-fallers, (Table 4.2). Binary logistic regression on the association between DTC and odds of falls was not significant (OR = 1.00, 95% CI 0.98-1.02, $p = 0.90$).

Table 4.2: Comparison of TUG, TUG-C, and DTC scores of people with Multiple Sclerosis based on prospective falls status, where faller = person with ≥ 2 falls.

<i>Outcome Measure</i>	<i>Fallers (n= 34)</i>	<i>Non-Fallers (n = 66)</i>
<i>Symbol Digital Modalities Test; mean (SD)</i>	33.53 (12.5)	32.39 (12.3)
<i>Timed Up and Go (seconds); median [IQR]</i>	11.25 [4.8]	11.68 [7.53]
<i>Timed Up and Go Cognitive (seconds); median [IQR]</i>	12.4 [4.06]	13.93 [10.05]
<i>DTC (%); median [IQR]</i>	-12.12 [22.66]	-14.38 [20.88]

SD: Standard Deviation, IQR: Interquartile Range

Subjective Measure of DTC (yes/no question about difficulty doing two things at once)-

A significantly higher percentage of fallers (65%) subjectively reported problems with dual tasking during their initial assessment compared to non-fallers ($p=0.01$), Table 4.3. The risk of falling was doubled if the participants reported problems with dual tasking with an associated risk ratio of 2.07 (CI 1.15, 3.71).

Table 4.3: Comparison of self-reported problems dual-tasking between fallers and non-fallers, where faller = person with ≥ 2 falls.

<i>Self-Reported Problems with Dual-Tasking</i>	<i>Faller (N = 34)</i>	<i>Non-Faller (N = 66)</i>	<i>P Value</i>
<i>Yes; N (%)</i>	22 (64.7)	25 (37.9)	<i>0.01</i>
<i>No; N (%)</i>	12 (35.3)	41 (62.1)	

Patterns of CMI

Analyses on pattern of CMI were performed for the 88 participants that had that data (Table 4.4). Differences between fallers and non-fallers was significant for those using pattern No. 6 (changes in gait, numbers correct) ($p=0.03$). An increased risk of falling was highest for those using pattern No.6 (RR=1.82, CI 1.09,3.04) and those using pattern No.1 and 2 had a protective effect and were more likely to be non-fallers. As seen in Figure 4.1, the most commonly used patterns amongst the whole group were No.3 (changes in gait, numbers incorrect) and No.6 (changes in gait, numbers correct). The least common pattern was No.5 (synchronise step and think) which involved the participant taking a step at the same time as saying the number.

Table 4.4: Between-group comparison of percentage of fallers (person with ≥ 2 falls) and non-fallers based on pattern of CMI (n= 88, not assessed for first 12 participants. Some participants used more than one pattern, n= 2 used 2 patterns, n= 1 used 3 patterns).

Falls Status	Pattern 1	Pattern 2	Pattern 3	Pattern 4	Pattern 5	Pattern 6	Total
Faller; N (%)	4 (12.1)	5 (15.2)	10 (30.3)	5 (15.2)	0 (0)	12 (36.4)	33 (100)
Non-Faller; N (%)	12 (21.8)	14 (25.5)	12 (21.8)	4 (7.3)	5 (5.1)	9 (16.4)	55 (100)
P Value	0.254	0.255	0.374	0.286	0.152	0.033	N/A
Risk Ratio (95% CI)	0.62 (0.25, 1.52)	0.65 (0.29, 1.45)	1.30 (0.74, 2.29)	1.57 (0.81, 3.02)	N/A	1.82 (1.09, 3.0)	N/A

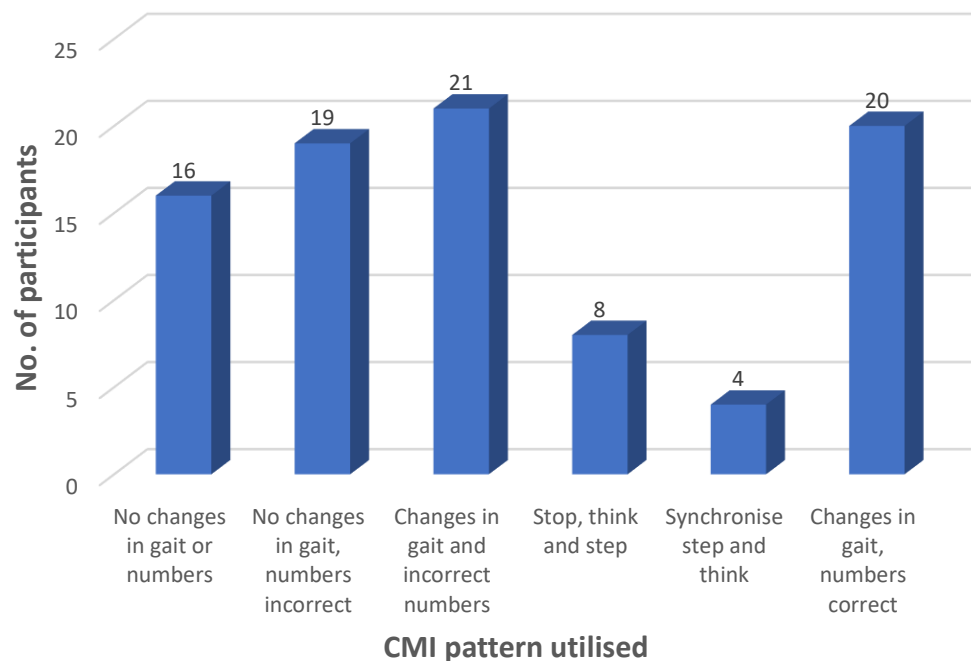
CMI: cognitive motor interference.

Pattern 1: no changes in gait, numbers correct, Pattern 2: no changes in gait, numbers incorrect,

Pattern 3: changes in gait, numbers incorrect, Pattern 4: stop, think and say number, take step, Pattern

5: synchronise step and think, Pattern 6: changes in gait, numbers correct

Fig 4.1: Cognitive Motor Interference (CMI) Patterns Utilised Amongst Whole Group



Discussion:

The primary objective of this study was to investigate if objectively measured DTC, calculated as the percentage change between the TUG and TUG-C, was associated with falls status in people with MS, and the results suggest that there is no association. The subjective measure of DTC examined by asking the question ‘do you have problems doing two things at once’ showed a significant difference between fallers and non-fallers and demonstrated that participants who report problems dual tasking are at twice the risk of falling when compared to those without problems dual tasking. Six distinct patterns of CMI were identified among this cohort of older people with MS and there was a significant difference between fallers and non-fallers and an increased risk of falls for those using pattern No. 6 (changes in gait, numbers correct). As the mean age of this study cohort is 52.6 years, they are already starting to experience the natural processes that occur with ageing and affect one’s strength and mobility such as decreased muscle mass, decreased coordination, slower speed of movement and increased movement variability (Seidler *et al.* 2010). Overall the age-related changes in the musculoskeletal system will be heightened in this MS cohort who already have dysfunction of the central and peripheral nervous system affecting mobility and activity performance, with falls being just one of the detrimental consequences. Problems such as falls and their sequela become more severe as the person with MS ages and these difficulties have been shown to be age related and age accelerated (Trojano *et al.* 2002).

The findings of this study regarding objectively measured DTC and falls status are consistent with previous findings from a comparable study population that similarly used a change in gait velocity during a mobility assessment to measure DTC (Gunn *et al.* 2013a). Another more recent prospective study that also used change in gait velocity to measure DTC but with a study population with relapse-remitting MS (RRMS) only and a milder disability level additionally found DTC was unable to predict future falls (Tajali *et al.* 2017). In contrast to these findings, a study using static posturography and electronic walkways found that both the DTC of cognitive performance and of walking velocity was associated with an increased risk of recurrent falls among people with MS (Etemadi 2016). However, the latter study had some noteworthy methodological differences when compared to the other studies. The study population was younger with a shorter disease duration and had significant methodological differences using more detailed and objective measures in the form of static posturography for balance assessment, electronic walkway for gait assessment and correct response rate (response rate per second multiplied by percentage of correct responses) as the measure of cognitive performance whereas the other studies including this one, only used simple timed walks when assessing DTC. However, it is often the more simple measures that can be easily performed without the use of expensive equipment that translate across to everyday clinical practise.

Our finding that DTC does not predict falls in MS differs to those of studies examining this concept in other populations. A study of over 1000 older adults found that an objectively measured DTC of 18% or more prospectively predicted fallers (OR = 1.07; CI 1.04, 1.10) (Yamada *et al.* 2011) but a recent systematic review has concluded that further prospective studies of older adults are needed to develop recommendations for

dual task testing as part of a multi-faceted falls risk assessment (Muir-Hunter and Wittwer 2016). In subacute stroke patients dual task assessment of gait has demonstrated an altered stride length and step length in fallers versus non-fallers (Baetens *et al.* 2013) and a longitudinal study of people with Parkinson's disease demonstrated that motor DTC significantly predicted future fallers with a sensitivity of 71%, specificity of 77% and 2.6 higher odds of being a future faller (Heinzel *et al.* 2016). A prospective study examining prediction of falls and near falls in people with mild Parkinson's disease included a subjective question about dual tasking similar to our self-report measure of problems dual tasking and simple logistic regression showed a self-report of balance problems while dual tasking had an odds ratio of 4.0 for predicting falls/and or near falls (Lindholm *et al.* 2015).

To the knowledge of the authors, this is the first study that investigated if self-reported problems with dual tasking were linked to falls status in people with MS. Previous research among older people with MS has asked about problems with concentration and forgetfulness (Finlayson *et al.* 2006; Peterson *et al.* 2008) and qualitative interviews have identified situations that require divided attention as a factor related to falls (Nilsagård *et al.* 2009), but no research to date has specifically asked about the participant's difficulties in doing two things at once. This concept of asking a simple question to help identify falls risk has been previously demonstrated in MS with regard to history of falls (Cameron *et al.* 2013) and in older people where health professionals are advised to routinely ask simple questions about fall history, fear of falls and feelings of unsteadiness as a quick falls risk screening tool (Stevens and Phelan 2013). In this study, a significant difference was identified between fallers and non-fallers in relation to subjectively reported problems with dual tasking. One possible reason for

this finding may be that when individuals are subjectively reporting problems with dual-tasking they are considering all dual-tasks that occur in their daily routine, whereas objective measures of dual-tasking ability only look at one dual-task activity in a controlled setting. A recent review (Leone *et al.* 2015) determined that most dual-task tests in the MS population were conducted at a self-selected speed, similar to the task in this study. However, it is suggested that these tests are not representative of activities of daily living, when people are more likely to be carrying out tasks at a heightened speed and in novel environments, which is likely to place a higher demand on motor and cognitive resources. Therefore, asking people with MS if they have problems doing two tasks at the same time may provide more accurate information regarding the patients' dual-tasking ability, and subsequently their falls risk, than attempting to objectively measure it.

While patterns of CMI have been examined in other neurological conditions such as stroke and PD (Kelly *et al.* 2012; Plummer *et al.* 2013) this is the first study to research patterns of CMI and falls status in MS. Previous research examining the effect of dual task activities in people with MS demonstrated significant deteriorations in gait with an added cognitive task, including altered swing time variability, increased double support time and a large decrease in gait speed (Hamilton *et al.* 2009; Sosnoff *et al.* 2011). Differences between fallers and non-fallers adopting each pattern of CMI in this study were significant for Group 6 (changes in gait, numbers correct). This subgroup, along with Group 3 (changes in gait and incorrect numbers), was one of the most common patterns utilised by participants and this may suggest that people with MS are not prioritising the different components of a complex task appropriately similar to what has been observed in people with Parkinson's disease (Bloem *et al.*

2006). This may be as a consequence of the limited processing capacity of the brain as highlighted in the attentional capacity theory and the bottleneck theory that have both been used to explain CMI behaviour (Wajda *et al.* 2017). However, these results should be interpreted with caution as there were small numbers in each of the subgroups using each type of pattern and a much larger sample would need to be analysed to draw any strong conclusions.

There were several strengths to this study including a large sample size, a very low attrition rate, and use of the gold-standard recommendations of a specific falls definition and prospectively recorded falls data (Coote *et al.* 2014) for a three month period. However, the findings from this study should be interpreted with consideration of its limitations. The progressive nature of this study cohort with median EDSS score of 6, limits the generalisability of the findings and results may not be applicable in a milder MS cohort. The cognitive task chosen was one of serial subtraction but it has been suggested that verbal fluency tasks may be more appropriate when assessing dual task cost in MS (Learmonth *et al.* 2017) and the investigators had no knowledge of baseline arithmetic competency levels of the participants. To fully investigate DTC both the cognitive and motor task should be assessed under single and dual task conditions (Plummer and Eskes 2015) but only the motor task was assessed under single task conditions in this study. Indeed, this seems to be a common issue in MS studies examining dual task cost as very few studies to date (Hamilton *et al.* 2009; Allali *et al.* 2014; Etemadi 2016) have actually reported the single task performance of the cognitive task and examined the DTC of cognition as well as motor function. No instructions were given to participants regarding task prioritisation and this study used the TUG as a measure of mobility while other studies measure objective balance

control (Etemadi 2016) or different versions of timed walks (Gunn *et al.* 2013a; Tajali *et al.* 2017). It has been advised that dual task assessment needs to be standardised to facilitate comparison of results from different studies that will strengthen the evidence base and allow for clearer recommendations (Plummer and Eskes 2015; Learmonth *et al.* 2017). Finally, the classifications of pattern of CMI used in this study may be considered a methodological limitation. Due to a lack of previously reported patterns of CMI for people with MS the six patterns of CMI utilised were identified through observing the patterns of the first 12 study participants but this method may have missed later characteristics that were not observed in that small initial sample.

Conclusion:

The findings of this study suggest that objectively measured DTC is not associated with falls status in a more progressive MS cohort who are relatively “young” but presenting with falls at a rate greater than “older” people. The subjective measurement of dual tasking ability is related to falls status and may be an easy method of screening for falls risk. Simply asking if they have a problem performing two tasks at once is a quick, easy and cost-free method of establishing dual-tasking ability and may be a useful adjunct in evaluating falls risk. Additionally, differences appear to exist between fallers and non-fallers based on whether they prioritise their cognitive or motor task under dual-task conditions. Future research involving more robust analysis and classification of patterns of CMI in a larger sample with a standardised method of DTC assessment will give a clearer insight into the role of DTC and CMI in falls risk assessment and its potential relevance as a component of falls interventions for people with MS.

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Chapter 5:

Development of a Falls Risk Prediction Tool for people with Multiple Sclerosis

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Authors' Contributions:

The author of this thesis (GQ) contributed to the paper as follows-

- Participated in study concept and design.
- Liaised with Chris McGuigan to aid participant recruitment.
- Clinic based assessment, collection of prospective falls diaries and data collection.
- Analysed the data using SPSS with guidance from Ailish Hannigan.
- Wrote the paper and submitted for publication.

LC assisted with data collection and manuscript preparation. RG assisted with manuscript preparation. AH gave guidance and advice regarding appropriate statistical methods to use. CM participated in study concept and design and assisted with participant recruitment. SC participated in study concept and design and assisted with manuscript preparation. All authors read and approved the final manuscript

Abstract:

Purpose: to determine which combination of variables has the highest sensitivity and predictive validity for identifying falls risk in people with Multiple Sclerosis.

Methods: in this prospective cohort study, consecutive patients attending an outpatient Multiple Sclerosis clinic (n=100), with Expanded Disability Status Scale score of 3-6.5 completed baseline assessment and falls diaries for the subsequent three-month study period. Outcome was rate of falls, and predictors were Timed Up and Go, Symbol Digit Modalities test, and self-report questions about various symptoms such as problems with fatigue, concentration, dual tasking, bladder and bowel control among others.

Results: There were 791 falls reported over the three-month period from a total of 56 fallers. Following multivariable regression analysis, the model with the greatest sensitivity (88%) and predictive validity (area under the receiving operating curve statistic = 0.72, 95% CI 0.62-0.82), included the variables of history of a fall, no visual problems, problems with bladder control and a slower speed on the Timed Up and Go.

Conclusion: this model is quick and easy to use in a clinic setting and could identify those at risk of falls, thus prompting earlier referral to appropriate falls prevention interventions.

Key Words: Multiple Sclerosis, Accidental Falls, Risk Assessment

Introduction:

Multiple Sclerosis (MS) is a progressive neurological condition with a diverse symptom presentation that includes lower limb weakness, spasticity and impaired balance (Francis 1997). Mobility and balance deficits present from an early stage of the disease (Martin *et al.* 2006) and impairments in balance and slower gait speed are associated with an increased risk of falls (Giannì *et al.* 2014). Falls are prevalent in this population with over 50% of people with MS falling in a three month period (Gunn *et al.* 2013a; Nilsagård *et al.* 2015) with participants reporting a wide range of falls from 1-63, and a high risk of injurious falls (Bazelier *et al.* 2011; Cameron *et al.* 2011). The number of falls required to be classified a “faller” varies but it has been argued that even one fall is significant with resulting loss of confidence and activity curtailment, and may indicate a transitional stage in relation to mobility and worsening disability (Matsuda *et al.* 2011) and hence a need for intervention.

While certain factors such as longer disease duration, impaired cognition, mobility aid use and fear of falling are known to be associated with increased falls risk in MS (Gunn *et al.* 2013b; Mazumder *et al.* 2015), no one particular falls risk tool suitable for everyday use in a clinic setting has been identified (Cattaneo *et al.* 2014). The assessment of balance is recommended in falls research (Cattaneo *et al.* 2014) but a recent systematic review found no currently used clinical balance measure has good discriminative ability or clinical utility for identifying falls risk (Quinn *et al.* 2017). One of the most commonly reported measures in that review was the Timed Up and Go and it demonstrated a significant difference between fallers and non-fallers in

retrospective study designs but did not predict falls in isolation (Quinn *et al.* 2018) suggesting multivariable models may be required to identify those at risk of falls and in need of intervention.

Discriminative ability refers to the ability of a measure to differentiate between fallers and non-fallers and is reported using the area under the receiving operating curve statistic (Moons *et al.* 2015). Clinical utility examines the usefulness of a specific test, usually in relation to patient outcomes and decision-making guidance, and is assessed using the summary estimates of sensitivity and specificity (Bossuyt *et al.* 2012). Previous studies using prospective falls diary recording have identified that detailed assessments such as the Physiological Profile Assessment (Gunn *et al.* 2013a; Hoang *et al.* 2014) and instrumented measures such as static posturography (Prosperini *et al.* 2013) show good predictive ability for falls status and good sensitivity in identifying falls risk. However, these complex assessments are time consuming and require specialist equipment and training, thus rendering them unsuitable for everyday use in a busy clinic setting. It has been demonstrated that simply asking about history of falls in the past has good predictive ability for identifying future falls risk (Cameron *et al.* 2013) and recently a prospective study identified that patient reported outcomes are more accurate than performance based measures for predicting future falls risk (Tajali *et al.* 2017) suggesting the need to add subjective reporting to objective measures of balance when assessing falls risk in MS.

Study Aim:

Thus, the aim of this study is to determine which combination of subjective and objective variables, has the highest sensitivity and predictive validity for identifying falls risk in people with MS. A falls risk tool of this type would allow the treating clinician to identify the risk of falls, communicate the level of risk to the individual, and refer onwards for appropriate falls prevention interventions in a timely fashion.

Methods:*Study Design:*

This was a prospective cohort study with falls status monitored using prospective diaries. The TRIPOD (Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis) statement was followed in the conduct and reporting of the study (Moons *et al.* 2015) (appendix 5.1). The study was approved by the associated University Ethics Committee and the associated hospital Ethics and Medical Research Committee.

Participants:

Consecutive patients attending the MS clinic in a tertiary hospital were invited to participate in the study if they met the following inclusion criteria: (1) A neurologist confirmed diagnosis of MS, (2) Expanded Disability Status Scale (Kurtzke 1983) of between 3.0 and 6.5 indicating some walking limitations but an ability to ambulate

independently (with or without an aid), (3) adequate cognitive function (as deemed by the treating physician) to participate in the assessment and falls diaries for the three-month study period. Participants under 18 years, pregnant woman or individuals unable to provide informed consent were excluded from the study. Recruitment and participant assessment was carried out between November 2014 and March 2016 with the final falls diaries collected in June 2016.

Outcome:

The outcome was falls incidence as reported using prospective falls diaries for a three-month period. Participants were provided with stamped addressed envelopes and falls diaries to be returned monthly. Those not returning their diaries were contacted by the researcher to remind them or to collect the data for that month by phone. Participants also had the option of a text or e-mail reminder to be sent fortnightly to optimise falls reporting. A fall was defined as ‘an unexpected event in which you come to rest on the ground, floor, or lower level’ (Lamb *et al.* 2005). There are a variety of classifications for faller status currently utilized in the literature (Matsuda *et al.* 2011), and in this study a faller is defined as a person with one or more falls in the three month diary period as recommended by the International MS Falls Prevention Research Network (Coote *et al.* 2014). This was chosen as it only takes a single fall to cause associated consequences such as fear of falling and activity curtailment, additionally history of a single fall is predictive of falling in the future (Cameron *et al.* 2013).

Predictors:

Data collected routinely at the clinic was incorporated into the data set for the study and included the Expanded Disability Status Scale score (level of disability), age, disease duration, self-reported falls in the preceding 3 months, current medications, type of MS and walking aid(s) used. Information was also collected on various symptoms and their level of interference with daily activities such as depression, pain, visual impairment and leg weakness. Additionally, the Symbol Digit Modalities Test, a brief assessment of cognition where participants try to match as many numbers and symbols as possible based on a given key in a 90 second test period, was used. The Symbol Digit Modalities Test demonstrates good sensitivity and discriminative ability in MS populations (Drake *et al.* 2010). Consenting participants then completed a falls screening questionnaire (appendix 5.2) that was developed following a literature review at time of study design that identified all retrospective and prospective cohort studies and any factor with a statistically significant odds ratio for falls status was included. The questionnaire consisted of yes/no questions and enquired about problems with fatigue, bladder and bowel, balance, doing two things at once, sensory disturbance, concentration and forgetfulness, among others. The full data collection tool used for the cohort study is in appendix 5.3.

Participants then completed the timed mobility assessment, the Timed Up and Go under single and dual task conditions. The Timed Up and Go is widely used in clinical practice and has been shown to be both valid and reliable in MS populations (Sebastião *et al.* 2016; Bennett *et al.* 2017) and discriminates between fallers and non-fallers (Sosnoff *et al.* 2011; Kalron *et al.* 2017). The measures were performed in the same

standardised order for every participant and participants were advised to walk “as quickly and safely as possible” while in their usual footwear and using their usual mobility device (if applicable). The participant was seated in a standard height chair and was instructed to stand up, walk 3 metres to a specific mark on the ground, turn around, walk back and sit in the chair again. Timing began when the participant started to rise from the chair and ceased when he/she was seated in the chair after walking back. The participant had one practice trial and then three recorded trials, with a mean value for the three walks used for statistical analysis. The participant then did the Timed Up and Go under dual task conditions with an added cognitive task of counting backwards in multiples of three. The Timed Up and Go-Cognitive was assessed in the same standardised manner as the Timed Up and Go. Both the Timed Up and Go and Timed Up and Go-Cognitive have been recommended for use in MS research and clinical practice by the American Physical Therapy Association Evidence Database to Guide Effectiveness task force (Potter *et al.* 2014). Dual task cost (DTC) was calculated using

$$DTC = \frac{ST - (DT)}{ST} \times 100$$

where ST = single task (Timed Up and Go value) and DT = dual task (Timed Up and Go-Cognitive value) (Kirkland *et al.* 2015).

Statistical Analysis:

Data were coded, entered and analyzed using SPSS Statistics for Windows Version 22. Counts and frequencies were used to describe categorical variables and normality was assessed using the Kolmogorov-Smirnov test. For numeric variables independent

sample T tests were used to test for differences in normally distributed variables between fallers (≥ 1 fall) and non-fallers (no falls) and Mann-Whitney tests were used to test for differences in skewed distributions. The association between categorical variables was tested using chi-squared or Fisher exact tests. Variables were grouped into demographic variables, mobility status, medications, MS symptom interference, falls screening questionnaire data, dual tasking strategies and objective measures. All variables with a p value of ≤ 0.2 from bivariate analysis were considered for inclusion in the multivariable logistic regression analysis.

Model building was iterative and guided by interpretability, parsimony, the evaluation of the Wald statistic for each variable at each step and measures of goodness of fit and clinical utility. This method is recommended over stepwise methods using solely significance-based decision-making to improve the stability and quality of the final model when using small data sets (Steyerberg *et al.* 2000). Goodness-of-fit of the final reduced model was assessed using the Hosmer and Lemeshow test and the Nagelkerke R square value. Odds ratios and 95% confidence intervals (CIs) are reported, a 5% level of significance was used. Sensitivity and specificity were calculated to examine the clinical utility of the final model. The aim was to find the model with the highest sensitivity combined with goodness of fit. Receiver operating curve analysis was carried out to determine the area under the receiving operating curve statistic value. The area under the receiving operating curve statistic can have any value between 0 and 1 with a value of 0.5 representing chance, values between 0.7 and 0.9 representing moderate discrimination and a value of 1 representing perfect discrimination (Moons *et al.* 2015). Positive likelihood ratio was calculated using sensitivity/1- specificity and negative likelihood ratio was calculated using 1- sensitivity/ specificity (Riddle

and Stratford 1999). Falls rate per person-year was calculated using the following formula (Ibrahim *et al.* 2000): falls rate = (total number of falls/total number of person-days [all participants]) multiplied by 365.

Results:

The sample included 101 people with MS (67 female). One participant withdrew after the baseline assessment as they did not wish to monitor their falls using diaries for three months, so data was analysed for a total of 100 participants. There was a diary return rate of 99.7% with 791 falls reported over the three-month period from a total of 56 fallers with a median of 3 falls per faller (IQR 4, range of 1-164). Falls rate per person-year was 32.08 falls. Injurious falls were reported by 57% (n= 32) of fallers with a median of one injurious fall (IQR 2, range of 0-22) per faller. Demographic and clinical characteristics of the sample are reported in table 5.1.

Table 5.1: Demographic and Clinical Information for the Sample

Characteristic	All participants (n=100)
<i>Age (years); mean (SD) [range]</i>	52.6 (10.78) [29-78]
<i>Gender; n (%)</i>	
Male	34
Female	66
<i>MS Classification; n (%)</i>	
Primary Progressive	19
Secondary Progressive	53
Relapsing-Remitting	24
Benign	2
Unknown	2
<i>Use of a Walking Aid; n (%)</i>	
Yes	73
No	27
<i>EDSS; median [IQR], mean (SD)*</i>	6 (2), 5.3 (1.2)
<i>Time Since Diagnosis (years); median [IQR], mean (SD)</i>	14 [13.75], 14.2 (9.5)
<i>Fall in the Past 3 Months (retrospective self-report); n (%)</i>	
Yes	50
No	50
<i>TUG score (secs); median [IQR], mean (SD)</i>	11.56 [6], 13.5 (7.0)
<i>TUG Cog score (secs); median[IQR], mean (SD)</i>	13.35 [6.8], 16.0 (8.5)
<i>SDMT score; mean (SD)</i>	32.8 (12.3),
<i>DTC score; median [IQR], mean (SD)</i>	-13.2 [21.6], -19.2 (27.4)

SD: Standard Deviation, MS: Multiple Sclerosis, EDSS: Expanded Disability Status Scale, TUG: Timed Up and Go, TUG-Cog: Timed Up and Go Cognitive, SDMT: Symbol Digit Modalities test, DTC: Dual Task Cost, IQR: Interquartile Range

*Mean and SD are reported for variables that are normally distributed and both mean and medians with IQR are reported for variables that are not normally distributed.

After bivariate analysis there were 20 potential predictor variables with a p value ≤ 0.2 that were deemed suitable for further multivariable analysis (appendix 5.4). Age, Expanded Disability Status Scale, MS type, current health status, employment status, history of an injurious fall, number and type of walking aids, medication number and type, fatigue, leg weakness, pain, poor concentration, problems with bowel control, concerns about falling, osteoporosis diagnosis, reduced sensation, fine motor problems, Timed Up and Go-Cognitive, dual task cost, and Symbol Digit Modalities

Test were all excluded from regression analysis. Gender had a borderline p value of 0.21 but was included as an association has been demonstrated between gender and falls risk previously (Nilsagård *et al.* 2015). Further variables were excluded from the reduced set of 20 after assessing for collinearity and the final covariates deemed suitable for inclusion in the model building process were male gender, MS course over the past year, retrospective reporting of a fall in the past, mobility aid use, subjective reporting of problems with balance/mobility, depression, not having a visual problem, problems with bladder control, stiffness/spasms in the limbs, subjective reporting of problems dual tasking, Timed Up and Go score. Table 5.2 shows the full model for regression analysis with all eleven variables included.

Table 5.2: Full Model for Logistic Regression Analysis (n= 100) to Predict Fallers

Predictor	Non - Fallers (N= 44)	Fallers (N= 56)	B	S.E	Wald	df	P value	Odds Ratio (95% CI)
Male Gender	12 (27.2%)	22 (39.3%)	0.94	0.55	2.88	1	0.09	2.56 (0.87, 7.58)
Deteriorating MS course past year	19 (43%)	35 (65%)	0.70	0.57	1.52	1	0.22	2.02 (0.66, 6.19)
Fall in the past 3 months	15 (34.1%)	35 (62.5%)	1.05	.53	4.04	1	0.05	2.88 (1.03, 8.08)
Use of a mobility aid	29 (65.9%)	44 (78.6%)	0.43	0.60	0.51	1	0.47	1.54 (0.47, 5.02)
Problems with balance/ mobility	44 (100%)	56 (100%)	0.27	0.52	0.28	1	0.60	1.31 (0.48, 3.61)
Depression	14 (31.8%)	26 (46.4%)	0.72	0.53	1.84	1	0.18	2.06 (0.73, 5.85)
No visual problems	29 (65.9%)	45 (80.4%)	1.72	0.62	7.70	1	0.01	5.59 (1.66, 18.82)
Problems with bladder control	28 (63.6%)	46 (82.1%)	0.60	0.58	1.06	1	0.30	1.81 (0.59, 5.62)
Stiffness or spasms	33 (75%)	48 (85.7%)	0.10	0.69	0.02	1	0.89	1.10 (0.29, 4.22)
Problems dual tasking	16 (36.4%)	31 (55.4%)	0.59	0.53	1.26	1	0.26	1.80 (0.65, 5.04)
TUG	11.19 IQR5.2	11.99 IQR7.7	0.01	0.03	0.11	1	0.75	1.01 (0.95, 1.08)

MS; Multiple Sclerosis, TUG: Timed Up and Go, IQR: Interquartile Range

Table 5.3 shows the final model with four predictor variables, a sensitivity of 88% and a specificity of 46%. The area under the receiving operating curve statistic of this final model was 0.72 (95% CI 0.62-0.82), see figure 5.1 for the receiver operating characteristic curve. The positive likelihood ratio was 1.63 and the negative likelihood

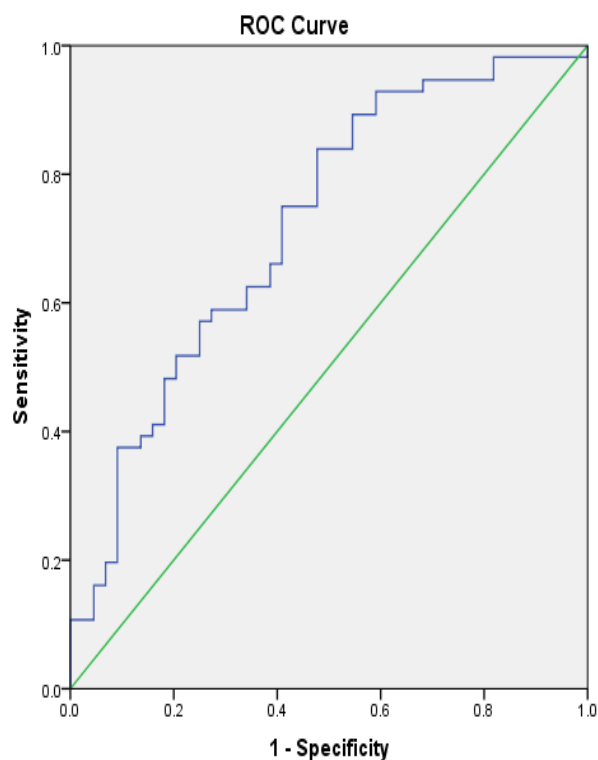
ratio was 0.26. The model had an adequate fit (Hosmer and Lemeshow test, $p=0.97$, Nagelkerke R Square =0.20). History of a fall in the past three months was associated with higher odds of falling (OR 3.33, 95% CI 1.38 to 8.03, $p= 0.008$). Not having visual problems was also associated with higher odds of falling (OR 2.90, 95% CI 1.06 to 7.90, $p= 0.038$).

Table 5.3: Logistic Regression Analysis, Final Model (n=100) to Predict Fallers

Predictor	B	S.E.	Wald	df	P value	Odds ratio (95% CI)
A fall in the past 3 months	1.20	0.45	7.13	1	0.01	3.33 (1.38, 8.03)
No visual problems	1.06	0.51	4.31	1	0.04	2.90 (1.06, 7.90)
Problems with bladder control	0.90	0.51	3.20	1	0.07	2.47 (0.92, 6.64)
TUG	0.02	0.03	0.38	1	0.54	1.02 (0.96, 1.08)

Sensitivity = 88%, Specificity = 46%, AUC = 0.72 (95%CI 0.62-0.82), TUG: Timed Up and Go

Figure 5.1: ROC Analysis of the Final Model, AUC = 0.72.



Discussion:

This prospective cohort study is the first study in MS to report the sensitivity and predictive validity of a simple falls screening tool suitable for use in a busy clinic setting. Fifty-six people had a total of 791 falls, of which 94 were injurious confirming the significance of the problem of falls for people with MS. The findings demonstrate that a model containing the predictor variables of a fall in the past 3 months, problems with bladder control, no visual problems and Timed Up and Go score is suitable for use as a falls screening tool with a sensitivity of 88% and an area under the receiving operating curve statistic value of 0.72. This is more sensitive than the Timed Up and Go alone which demonstrated an area under the receiving operating curve statistic value of 0.60 and sensitivity of 82% when used in isolation for falls risk prediction in people with MS (Quinn *et al.* 2018). While the sensitivity and discriminative ability of the model are reasonably good, the specificity is low (46%) indicating that some non-fallers may be incorrectly identified as fallers and referred for in-demand resources that they may not actually need. However, in a falls risk screening tool of this type it is more important to have high sensitivity and definitely capture the potential fallers than have a high specificity, as the intervention may be of benefit to non-fallers also and would certainly not be harmful.

History of a fall being predictive of future falls is not surprising and has been demonstrated to have good discriminative ability in previous studies among people with MS (Cameron *et al.* 2013) and in stroke survivors (Xu *et al.* 2018). The fact that not having a visual problem was an important predictor is in contrast to other studies where dynamic visual acuity and visual contrast sensitivity were not significantly

different between faller and non-faller groups (Gunn *et al.* 2013a; Hoang *et al.* 2014). However, both these studies assessed vision objectively whereas our study assessed vision by means of self-report only. A study involving qualitative analysis post interview found visual impairment was perceived by people with MS to be associated with falls (Nilsagård *et al.* 2009) but the types of visual impairment mentioned were double vision or impaired eye and movement coordination whereas in our study we simply asked if problems seeing interfered with typical daily activities. The fact that our results showed not having a visual problem increases falls risk appears counter intuitive but may be to do with increased confidence and risk-taking behaviour when no visual problems, whereas a person with an actual visual problem such as double vision may be taking extra precautions and adapting their behaviours in a way that helps to decrease their falls risk. Future research could explore this domain using both objective and self-report measures to determine if the different methods of assessment correlate.

Four previous prospective studies examined falls risk prediction in MS using a form of balance assessment, with two reporting area under the receiving operating curve statistic values ranging from 0.71 (Hoang *et al.* 2014) to 0.73 (Gunn *et al.* 2013a) and two reporting sensitivity values ranging from 80% (Kasser *et al.* 2011) to 88% (Prosperini *et al.* 2013) and specificity values ranging from 67% to 83% respectively. The former two studies used the Physiological Profile Assessment (Gunn *et al.* 2013a; Hoang *et al.* 2014) and the latter two used force plate assessment for the centre of pressure (Prosperini *et al.* 2013) and the Sensory Organisation Test (Kasser *et al.* 2011). Three of those studies used multivariable models (Kasser *et al.* 2011; Gunn *et al.* 2013a; Hoang *et al.* 2014) and one used balance assessment only (Prosperini *et al.*

2013). Our model's discriminative ability and sensitivity values compare favourably with those earlier models and includes measures that are simple and easy to use, require no specialist equipment or training and that may translate better to the real-life clinical setting. Methodological differences such as the variance in faller classification used and length of falls monitoring makes it difficult to truly compare these models with our findings. A prospective cohort study (Tajali *et al.* 2017) that also classified a faller as a person with one or more falls, found that patient reported outcomes are better at predicting fall risk than performance based measures, and this is confirmed in our prediction model.

For Parkinson's disease and stroke falls risk prediction models have reported varying levels of accuracy. A simple three step prediction tool in Parkinson's disease (including history of a fall, freezing of gait and slower walking speed) demonstrated high predictive validity with an area under the receiving operating curve statistic of 0.80 (Paul *et al.* 2013) and a model for stroke involving upper limb function and a history of near falls demonstrated a sensitivity of 60%, specificity of 70% and an area under the receiving operating curve statistic of 0.69 (Ashburn *et al.* 2008). However, an external validation study examining the latter model and a second model involving falls history and balance assessment using the Berg demonstrated poor discriminative ability for both models with area under the receiving operating curve statistic values of 0.55 and 0.56 respectively (Walsh *et al.* 2017). A prospective study with a 6 month follow up period involving people with MS, Parkinson's disease and stroke found that risk of falls is associated with disease type with Parkinson's disease having the highest risk, followed by MS and that balance confidence measured with the Activities-specific Balance Confidence scale is a common predictor of falls for the 3 conditions

(Beghi *et al.* 2018), highlighting the importance of self-report measures when identifying falls risk in these patient cohorts.

In community-dwelling elderly populations, numerous models and risk assessment tools have been proposed but a recent systematic review and meta-analysis (Lusardi *et al.* 2017) found that no single test or measure demonstrated strong post-test probability values (incorporating sensitivity, specificity and likelihood ratios). That review suggests that combining simple medical history questions (including history of falls and fear of falling) with a self-report measure and a performance based measure (including the Timed Up and Go) may be the most reliable type of tool to use and the model proposed in this study is in line with that recommendation, though adding a measure of fear of falling or balance confidence may further enhance its discriminative ability and clinical utility.

Study Limitations:

The strengths of this study include the robust methodology including use of prospective falls monitoring and clear reporting of both discrimination and clinical utility. A possible limitation is that our cohort had predominantly progressive MS and our findings may not be applicable in milder, relapse-remitting cohorts. However, more progressive disease is strongly associated with an increased falls risk (Gunn *et al.* 2013b; Giannì *et al.* 2014) and these are the individuals most in need of falls interventions. The sample size of 100 was determined based on previous falls research in MS (Gunn *et al.* 2013a; Prosperini *et al.* 2013) and was considered a feasible and realistic recruitment target, however the wide confidence intervals for the odds ratios

reflect the uncertainty in the estimates and are a limitation of the study. The percentage of variance not explained by our final model indicates that other factors not considered in our data set could potentially affect falls risk and should be examined in future research. These factors may include psychosocial variables such as low falls self-efficacy and level of falls control that have been shown to be common in people with MS (Comber *et al.* 2017) and other co-morbidities and personal/environmental factors. More detailed assessment of common symptoms in MS such as pain and sensory disturbance is warranted as somatosensory impairment has been shown to be associated with limited balance in MS (Jamali *et al.* 2017) and leg pain was significantly associated with frequent falls in previous prospective research (Hoang *et al.* 2014). We found no difference between fallers and non-fallers in cognition but the cognition measure used in our study is a quick screening tool for assessing information processing speed (Schependom *et al.* 2014) whereas a more detailed cognitive test that incorporates verbal function, memory and executive function may have provided more useful information (Chiaravalloti and DeLuca 2008) .

Conclusion:

A falls risk model including the self-report variables of history of a previous fall, problems with bladder control, no visual problems and the objective measure of the Timed Up and Go has reasonably good discriminative ability and sensitivity for identifying falls risk in people with MS with an area under the receiving operating curve statistic value of 0.72 and a sensitivity of 88%. This model does not need any specialist equipment or training and is quick and easy to carry out in a typical real-life

clinical setting. Future research needs to explore what other potential factors might improve the accuracy of this model and external validation with people of varying MS subtypes is needed to support its use in a wider context.

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Chapter 6:

Exploration of the Variance

of the Model

Introduction:

In preceding chapters the extent of the problem of falls in MS has been discussed and the high prevalence of falls in this condition (Nilsagård *et al.* 2015) and the detrimental consequences associated with falls such as injury, fear of falls, activity curtailment and subsequent deconditioning (Peterson *et al.* 2008; Cameron 2011; Kasser *et al.* 2014) have been highlighted. The primary aim of this thesis was to develop a falls risk model for people with MS (see chapter five) suitable for use in a busy, clinic setting and requiring no specialist training or equipment. The resulting model from a prospective cohort study includes the variables of history of a fall, no visual problems, problems with bladder control and a slower speed on the Timed Up and Go (TUG). This model has reasonably good sensitivity (88%) and predictive validity (area under the receiving operating curve statistic, AUC, = 0.72 95% CI 0.62-0.82), but the specificity is low (46%) and it explains only a small amount of variance with a Nagelkerke R Square value of 0.20.

To help inform future research and determine what other variables should be added to the model to improve accuracy, data from three different sources (post hoc exploration of existing data sources within the MS research team at University of Limerick) were examined - firstly the output from a literature review of studies using prospective falls monitoring in MS, secondly the additional data on causes and consequences of falls from three months of falls diaries collected as part of the main longitudinal study (see chapter five), and finally a content analysis on qualitative data collected from

clinicians' interviews where participants were asked their opinions on present and future falls interventions and discussed what they thought caused falls.

Thus, the aims of the analysis in this chapter are to:

- 1) Conduct a narrative review of all studies using prospective monitoring of falls in MS to identify other potential predictor variables that might be suitable for inclusion in a falls risk model.
- 2) Examine the data from three months of falls diaries specifically looking at context and causes of falls to determine if any useful information relevant to a falls risk model.
- 3) Explore the themes arising from a content analysis of clinicians' interviews focusing on aspects related to falls risk assessment and treatment prioritisation to determine type of assessments currently in use and what may translate well to clinical practice.

Methods:

Method A- Narrative Review:

The first source of data examined was the current evidence base in relation to falls risk prediction for people with MS and all studies using prospective falls monitoring were included. The literature search was first carried out in March 2018 and updated in July 2018. The search terms utilised were "Multiple Sclerosis" AND Fall* OR "Accidental

Fall” OR Slip OR Trip OR Imbalance OR “Postural control” OR “Postural instability” OR perturbation OR “postural sway” AND Risk OR Predict*OR Correlat* OR Associati* OR Screen* OR Probability. Databases searched included Ebsco (Academic Search Complete, AMED, CINAHL, Medline, PsychArticles, PsychInfo, SportDiscus, Biomedical Reference Collection), Scopus, Web of Science and Embase.

The inclusion criteria for the study selection process were confirmed diagnosis of MS, ambulatory with/without an assistive device, prospective cohort/longitudinal studies, peer reviewed journal articles. Review papers were excluded. If there was any uncertainty about a study, it was discussed with my primary supervisor (SC) until consensus was reached. Data was extracted from the studies to populate an excel spreadsheet including information on study numbers, fall definition, faller classification, follow up period, predictor variables, sensitivity and specificity, AUC values, odds ratio values. All predictor variables and models were then included in a table examining the discriminative ability, clinical utility and odds ratio of the variables in question.

Method B-Data from the 3 months of falls diaries:

In order to examine other factors that hadn’t been considered in the model the data from prospective falls diaries was analysed. These diaries were used to record falls during a three-month period as part of a larger study involving combining objective measures with clinical variables to develop a falls risk prediction tool for people with MS (chapter five). The study was approved by the University of Limerick Ethics

Committee and the St. Vincent's Healthcare Group Ethics and Medical Research Committee.

Data from the falls diaries was examined to further explore the consequences of falls such as increased healthcare utilisation and to help determine who should be targeted for falls prevention interventions i.e. any faller, frequent fallers, injurious fallers. The falls diaries collected information on the number of falls and number of injurious falls per month, number and type of injuries per month, presence of any relapses, medical services utilised due to a fall, presence of a long lie and if any assistance was required to get up from the floor. Ecological validity is gaining increasing importance in relation to clinical measures and time/location of assessment may be relevant when using a falls risk tool. Therefore, for the first two falls of any given month the participant was asked to document the time and location of the fall and what they think caused them to fall (multiple responses permitted for causes of fall, participants could tick the relevant choice from a list of 16 potential causes). An example of a monthly falls diary is at the end of this thesis, see Appendix 6.1.

Participants were given stamped addressed envelopes to return the diaries at the end of each month to the study site and were also given the option of a fortnightly text or email reminder to optimise the return rate. Telephone follow up was used to clarify any missing information. Information relating to the circumstances and context of falls was examined for any potential variables that may be relevant to a falls risk prediction tool. Data was extracted into Excel and analysed using excel and SPSS software, version 22.

Method C-Content analysis of data from clinicians' interviews regarding falls prevention interventions:

This section reports a post-hoc analysis of previously conducted semi-structured interviews carried out with 12 clinicians as part of a larger research study developing fall prevention interventions carried out by colleagues on the MS research team in University of Limerick. This study was reviewed and approved by the University of Limerick ethics committee. Clinicians were asked about their opinions in relation to current and future falls prevention interventions including current interventions used, barriers and facilitators, feasibility of future interventions. For this analysis data in relation to falls risk assessment was the focus.

Participants were recruited through national physiotherapy and occupational therapy networks via an email invitation and the interviews were carried out over the phone or in person depending on location of the participant with each interview lasting approximately 60 minutes duration. The aim was to have a mix of experienced and non-experienced clinicians across a range of work settings, this purposeful sampling was undertaken to collect data from clinicians who regularly (n=5) and irregularly (n=7) worked with people with MS to provide valuable information in terms of falls risk assessment, intervention content and intervention feasibility. Interviews were conducted until data saturation was reached. The interviews were recorded, and notes were taken throughout by the researchers. The interviewees were provided with a summary at the end of the interview and given the opportunity to amend or add to the key points from the interview. The interviews were transcribed verbatim and imported onto a qualitative analysis software programme, NVivo 11.

The analysis for this chapter was a secondary post-hoc analysis of the data to specifically find codes that might help inform and refine future falls risk models further. Analysis followed the six steps outlined by Braun and Clarke (2006) which include familiarisation with the data, generation of initial codes, searching for themes, revision of themes, definition and naming of themes and provision of the written report. Themes involving falls risk assessment were specifically examined. Treatment prioritisation and barriers were also explored. The results from this secondary analysis were cross checked by a second member of the research team to ensure credibility of the data, by allowing more in-depth analysis and more detailed interpretation of findings.

Results:

Results A-Narrative Review:

Initially there were 24,541 papers, after duplicate removal there was 20,743. After scanning the abstracts 47 full texts were read in detail and after applying the inclusion criteria there were 26 studies suitable for inclusion in the review. The combined studies had a total of 3619 participants (74% female) and a range of MS subtypes with relapse-remitting MS the most common across all studies (55% of participants), followed by secondary progressive (29% of participants). There was heterogeneity evident in relation to study methodology with four different faller classifications used, six different fall definitions, sample sizes ranging from 12 to 537 participants and a follow up period of falls monitoring ranging from seven weeks to one year. Multiple

risk factors were explored in these studies including clinical and instrumented measures of mobility and balance (see Table 6.1), self-report measures (Table 6.2) and cognitive and medication related factors (Table 6.3). Only five studies (Nilsagård *et al.* 2009b; Kasser *et al.* 2011; Cameron *et al.* 2013b; Gunn *et al.* 2013; Prosperini *et al.* 2013) reported sensitivity and specificity values for risk factors in relation to predicting falls and nine studies (Cameron *et al.* 2013b; Dibble *et al.* 2013; Gunn *et al.* 2013; Hoang *et al.* 2014; Hoang *et al.* 2016; Nilsagård *et al.* 2016; Tajali *et al.* 2017; Zelaya *et al.* 2017; Chinnadurai *et al.* 2018) reported area under the receiving operating curve (AUC) values. Of these studies, three reported on actual prediction models rather than individual variables (Kasser *et al.* 2011; Gunn *et al.* 2013; Hoang *et al.* 2014), see Table 6.2.

A further twelve studies (Nilsagård *et al.* 2009b; Gunn *et al.* 2013; Cameron *et al.* 2015; Mazumder *et al.* 2015; Nilsagård *et al.* 2015; Etemadi 2016; Nilsagård *et al.* 2016; Comber *et al.* 2017; Tajali *et al.* 2017; Tijisma *et al.* 2017; Zelaya *et al.* 2017; Gunn *et al.* 2018) reported on falls risk in terms of odds ratio. Seven of the included studies did not report indices of discrimination or clinical utility or risk in terms of odds ratio (Stephens *et al.* 2001; Cameron *et al.* 2013a; Kasser *et al.* 2014; Carling *et al.* 2016; Nilsagård *et al.* 2017; Vister *et al.* 2017; Cattaneo *et al.* 2018) but the studies in question did not have falls risk prediction as their main objective and rather were looking at falls in relation to other variables or at changes pre and post a specific intervention.

Table 6.1: Discriminative Ability, Clinical Utility and Odds Ratios of Clinical and Instrumented Measures of Mobility and Balance

Variable – measure used	Study Author/year	AUC value (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	Odds Ratio (95% CI)
Disability level- EDSS	Cameron 2013	0.60	NR	NR	NR
	Chinnadurai 2018	0.71 [0.60,0.83]	NR	NR	NR
	Nilsagard 2009	NR	48%	82%	1.99 [1.22,3.4]
	Gunn 2013	NR	NR	NR	0.81 [0.49,1.35]
	Nilsagard 2015- EDSS 6	NR	NR	NR	5.10 [2.08,12.47]
	EDSS 4	NR	NR	NR	5.30 [2.23,12.64]
	Dibble 2013	0.56 [0.36,0.77]	NR	NR	NR
Clinical measures mobility/balance- BBS	Dibble 2013	0.72 [0.52,0.89]	NR	NR	NR
	Nilsagard 2009	NR	94%	32%	0.94 [0.85,1.01]
	Prosperini 2013	NR	32% [18,48]	87% [75,94]	NR
	TUG				
	Dibble 2013	0.66 [0.46,0.86]	NR	NR	NR
	Tajali 2017	0.65	NR	NR	2.24 [1.17,4.28]
	DGI				
	Dibble 2013	0.68 [0.49,0.87]	NR	NR	NR
	FR				
	Dibble 2013	0.66 [0.47,0.84]	NR	NR	NR
DTC	Tajali 2017	0.48	NR	NR	0.99 [0.64,1.52]

		0.49	NR	NR	1.11 [0.72,1.71]
CSRT	Etemadi 2017	NR	NR	NR	1.23 [0.98,4.45]
	Gunn 2013	NR	NR	NR	1.0 [0.99,1.0]
	Tijmsma 2016	NR	NR	NR	1.69 [1.27,2.26]
T25FW	Tajali 2017	0.79	NR	NR	3.77 [1.86,7.63]
	Cameron 2013	0.71	NR	NR	NR
	Chinnadurai 2018	0.72 (0.61,0.82)	NR	NR	NR
FSST	Nilsagard 2009	NR	60%	75%	1.02 [0.98,1.09]
TUG C	Nilsagard 2009	NR	73%	54%	1.00 [0.95,1.08]
2MWT	Tajali 2017	0.71	NR	NR	0.44 [0.26,0.75]
6MWT	Nilsagard 2015	0.67 [0.50,0.83]	NR	NR	0.64 [0.40,1.03]
Instrumented Measures –					
Posturography	Cameron 2013	0.62	NR	NR	NR
	Prosperini 2013	NR	88% [74,96]	67% [53,78]	NR
Cervical VEMP	Chinnadurai 2018	0.82 [0.73,0.91]	NR	NR	NR
Ocular VEMP	Chinnadurai 2018	0.79 [0.68,0.91]	NR	NR	NR
Lower limb SEP	Chinnadurai 2018	0.73 [0.59,0.88]	NR	NR	NR
LOS	Kasser 2011 (2 faller classifications)	NR	65% (≥ 1 fall)	73%	NR

			76% (≥ 2 falls)	90%	NR
SOT	Kasser 2011 (2 faller classifications)	NR	80% (≥ 1 fall)	83%	NR
			67% (≥ 2 falls)	91%	NR
PPA	Gunn 2013	0.67 [0.58,0.76]	56%	74%	1.9 [1.34,2.69]
	Gunn 2018	NR	NR	NR	1.30 [1.17,1.46]
	Hoang 2016	0.64	NR	NR	NR
Leg strength using Biodex	Kasser 2011 (2 faller classifications)	NR	81% (≥ 1 fall)	56%	NR
			67% (≥ 2 falls)	91%	NR

AUC = area under the receiver operating characteristic curve statistic, EDSS = Expanded Disability Status Score, BBS = Berg Balance Scale, TUG = Timed Up and Go Test, FR = Functional Reach, DGI = Dynamic Gait Index, PPA = Physiological Profile Assessment, T25FW: Timed 25 foot walk test, 2MW: 2-minute walk, DTC: Dual Task Cost, FSST = Four Square Step Test, TUG-C = Timed Up and Go Cognitive, LOS = limits of stability, COG = centre of gravity, 6MWT = six minute walk test, CSRT = Choice Stepping Reaction time, VEMP = vestibular evoked myogenic potential, SEP = somatosensory evoked potential, SOT = sensory organisation test. CI = confidence interval, CI is stated when reported, NR = not reported.

Table 6.2: Discriminative Ability, Clinical Utility and Odds Ratio of Self Report Variables and Previous Models

Variable – measure used	Study Author/year	AUC value (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	Odds Ratio (95% CI)
Self-report – ABC	Tajali 2017	0.92	NR	NR	0.06 [0.02,0.18]
	Cameron 2013	0.69	NR	NR	NR
	Chinnadurai 2018	0.63 [0.50,0.75]	NR	NR	NR
	Dibble 2013	0.68 [0.48,0.87]	NR	NR	NR
	Gunn 2013	NR	NR	NR	1.01 [0.96,1.06]
	Tajali 2017	0.89	NR	NR	9.27 [3.93,21.9]
	Cameron 2013	0.66	NR	NR	NR
	Chinnadurai 2018	0.59 [0.47,0.72]	NR	NR	NR
	Gunn 2018	NR	NR	NR	1.05 [1.03,1.07]
	Mazumder 2015	NR	NR	NR	1.22 [1.04,1.43]
FES-I	Tajali 2017	0.91	NR	NR	11.85 [4.59,30.59]
	Cameron 2013	0.69	NR	NR	NR
	Chinnadurai 2018	0.62 [0.51,0.72]	NR	NR	NR
	Nilsagard 2009	NR	52%	82%	1.01 [0.98,1.04]
MSWS-12	Cameron 2013	0.75	89%	56%	NR
	Nilsagard 2009	NR	NR	NR	2.04 [0.8,5.3]
	Gunn 2013 (2 faller classifications)	NR (≥ 1 fall) NR (≥ 2 falls)	NR NR	NR NR	2.46 [0.89,6.83] 10.62

					[4.65,24.22]
	Chinnadurai 2018	0.64 [0.53,0.75]	NR	NR	NR
MFIS	Tajali 2017	0.87	NR	NR	7.32 [3.29,16.29]
Bladder dysfunction - general	Gunn 2013	NR	NR	NR	2.77 [1.4,5.48]
-specifically, urinary urgency with incontinence	Zelayna 2017	0.82	NR	NR	57.57 [3.43,966.05]
Integrated Measures/Mo dels-					
1) PPA, Ashworth, EDSS	Gunn 2013	0.73 [0.65,0.81]	69%	70%	NR
2)Sway with eyes closed, poor coordinated stability and decreased fine motor control (assessed with 9HPT)	Hoang 2014	0.71 [0.64,0.79]	NR	NR	NR
3)Different COG leans	Kasser 2011	NR	70%	71%	NR
4)COG motion	Kasser 2011	NR	71%	88%	NR

AUC = area under the receiver operating characteristic curve statistic, ABC = Activities specific Balance Confidence Scale, EDSS = Expanded Disability Status score, FES- I = Falls Efficacy Scale International, PPA = Physiological Profile Assessment, MSWS-12: 12-item multiple sclerosis walking scale, MFIS: modified fatigue-impact scale, 9HPT = nine-hole peg test, COG = centre of gravity. CI = confidence interval, CI is stated when reported, NR = not reported.

Table 6.3: Discriminative Ability, Clinical Utility and Odds Ratio of Cognitive and Medication related variables

Variable – measure used	Study Author/year	AUC value (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	Odds Ratio (95% CI)
Cognitive Measures- SDMT	Gunn 2013	NR	NR	NR	1.00 [0.97,1.05]
Medications- No of medications,	Cameron 2015	NR	NR	NR	1.13 [1.0,1.28]
	Gunn 2013	NR	NR	NR	1.01 [0.92,1.12]
Nervous system medications,	Cameron 2015	NR	NR	NR	1.43 [1.09,1.93]
Alimentary tract and metabolism medications,	Cameron 2015	NR	NR	NR	2.64 [1.20,7.23]
SSRI and SNRI antidepressants,	Cameron 2015	NR	NR	NR	1.96 [1.7,3.71]
DMTS (protective, ↓ risk of falls),	Cameron 2015	NR	NR	NR	0.52 [0.28,0.95]
Genitourinary and sex hormone medications,	Comber 2017	NR	NR	NR	5.15 [1.43,18.61]
Centrally acting muscle relaxants	Comber 2017	NR	NR	NR	5.18 [1.55,17.36]

AUC = area under the receiver operating characteristic curve statistic, SSRI = serotonin reuptake inhibitors, SNRI = serotonin-norepinephrine reuptake inhibitors, DMT = disease modifying therapy, SDMT = symbol digit modalities test. CI = confidence interval, CI is stated when reported, NR = not reported.

From Tables 6.1 and 6.2 above the most commonly reported variables are the Falls Efficacy Scale International (FES-I), Expanded Disability Status score (EDSS) and the 12-item Multiple Sclerosis walking scale (MSWS-12). The only four variables that

have sensitivity, specificity, AUC and odds ratio values all reported are the EDSS, MSWS-12, history of a fall and Physiological Profile Assessment (PPA). History of a fall is the only variable with a sensitivity of $> 80\%$, $AUC > 0.7$ and odds ratio > 1 , but across two different studies.

From the models reported only one reports sensitivity, specificity and AUC value and that model includes the PPA, Ashworth and EDSS (Gunn *et al.* 2013) and indeed that study, along with the study examining the variable of history of a fall (Cameron *et al.* 2013b) are the only two to report sensitivity, specificity and AUC values within the one study cohort.

The variables with an AUC value of ≥ 0.7 representing moderate discrimination include urinary urgency with incontinence, vestibular evoked myogenic potential, history of fall, the MSWS-12, the 2-minute walking test, the Activities specific Balance Confidence scale (ABC), FESI, EDSS, Berg Balance Scale (BBS), modified fatigue impact scale and timed 25-foot walk (T25FW) (reported in 3 studies). Two of the integrated models (one of PPA, Ashworth and EDSS; the other of sway with eyes closed, poor coordinated stability and decreased fine motor control) also demonstrate an AUC of ≥ 0.7 .

When looking at sensitivity values $\geq 80\%$, the relevant variables are history of a fall, posturography, the sensory organisation test, lower limb strength using the Biodex and

the BBS. None of these variables are reported with high sensitivity in more than one study.

If looking at odds ratios of ≥ 1.0 , the variables worth examining include the choice stepping reaction time, dual task cost (DTC), the PPA, modified fatigue impact scale, TUG, T25FW, urinary urgency with incontinence, general bladder dysfunction, history of a fall, nervous system medications, alimentary tract medications, anti-depressants, genitourinary medications, muscle relaxants, the FESI and EDSS. The FESI, EDSS, DTC, history of a fall and PPA are all reported with odds ratios of ≥ 1.0 in more than one study.

Results B- Data from the falls diaries:

Falls diaries were completed by 100 participants during the three-month study period. There was a diary return rate of 99.7%.

Falls and Injurious Falls: At the end of the study period there was a total of 791 falls (range from 1-164) reported from 56 participants. There were 94 injurious falls reported from 32 fallers (range of 0-22). There were 34 participants (61% of fallers) with 2 or more falls. The most common injuries were leg bruises (31%), arm bruises (26%) and arm cuts/scrapes (12%) with 6 people requiring medical attention due to a fall. There was only one significant injury in the form of a fracture. Of the top five most frequent fallers (range of 34-164 falls per faller), four reported injurious falls but none of those highly frequent fallers required medical attention. The faller with

the most injurious falls (22) did not require medical attention for injuries. Eleven participants reported an MS relapse during the study period with two participants reporting relapses in more than one month. 82% of those reporting a relapse were fallers. No participants had a long lie (greater than 60 minutes on the floor) but 34% of fallers did require assistance to get up from the floor.

Causes and Context of Falls: The most common cause of falls reported were poor balance (25%), weakness in the legs (22%) and fatigue (14%). Afternoon time (37%) was the most common time of day to fall, followed by evening (28%), with 24% of falls occurring in the morning and only 11% at night. Most falls occurred inside the home (63%), with 21% occurring outside the home and only 16% away from the home.

Results C- Data from the clinicians' interviews:

A total of 12 clinicians were interviewed from a variety of different work settings, see Table 6.4 with participant demographics. Only 2 participants had availed of specific falls training in the past. When asked how often they encounter people with MS (from their MS client base) who have experienced a fall or at risk of falling, 2 participants said often, 5 said always and 5 said sometimes.

Table 6.4: Participant Demographics for Clinician Interviews

Participant	Age	Gender	Years qualified	Setting of employment	Job title	Percentage MS clients
1	31	F	9	Hospital	Clinical specialist physiotherapist	100%
2	38	M	14	MS Society	Senior physiotherapist	100%
3	33	F	10	Hospital	Senior physiotherapist	33%
4	31	F	8	Primary Care	Senior physiotherapist	1%
5	35	F	10	Primary Care	Senior physiotherapist	70%
6	32	F	10	Hospital	Senior physiotherapist	10%
7	50	F	15	Primary Care	Senior physiotherapist	33%
8	28	F	6	Hospital	Senior physiotherapist	40%
9	36	F	12	Hospital	Practice physiotherapy tutor	5%
10	28	F	6	Hospital	Staff grade physiotherapist	10%
11	34	F	12	Primary Care	Senior physiotherapist	15%
12	31	F	8	Primary Care	Staff grade occupational therapist	5%

After the stages of open and axial coding the refined themes identified were: dimensions of assessment in falls prevention, dimensions of intervention for falls prevention, barriers and facilitators to implementing falls prevention programmes. When looking more closely at the content of the data in relation to falls risk assessment, some of the most common topics mentioned include fall cause (9 out of 12 sources), balance assessment (11 out of 12), strength assessment (5 out of 12), cognitive function (7 out of 12), fall frequency (6 out of 12), fall characteristics (4 out of 12) and environmental assessment (4 out of 12).

In relation to objective assessment balance and strength were frequently discussed-

‘So again, having your assessment is important and then if they have minor balance or mobility problems or strength problems you would try address those before they become bigger problems or before they fall’. (Participant 1)

In relation to balance and gait certain outcome measures were mentioned extensively including the Berg Balance Scale, Dynamic Gait Index, the Mini Best test and the Tinetti. In relation to fear of falls and self-report measures, the only one mentioned was the Falls Efficacy Scale International.

Environmental assessment and continence issues were also deemed to be important-

‘there’s you know an environmental assessment, everything is kind of looked at so medications are looked at, vision is looked at, the environment is looked at, there’s a balance assessment done on the person am we look at things like continence so in a case that someone was rushing to the toilet and that’s why they fell or am and then kind of looking at their support network that kind of thing.’ (Participant 7)

Cognitive assessment and the role of cognitive impairment emerged as an important topic in relation to dual tasking and cognitive motor interference, and how that may affect falls -

‘I use it at the moment like I think dual tasking is a big thing and especially with patients who would have cognitive problems’ (Participant 1)

Asking about falls at all stages of the disease and highlighting the importance of falls risk assessment and falls prevention for GPs and Neurologists was also discussed, emphasising the need for falls risk assessment at an early stage of the disease in order to ensure earlier intervention and prevention of further deterioration at later stages-

'I suppose I would always ask even new diagnosis or people who would have mild disabilities about falls or near falls just to pick up on problems that hopefully we can prevent and stop them from becoming a bigger problem.' (Participant 1)

Using a person's falls risk as a potential screening criteria and prioritisation criteria to access services was identified and may be one method of facilitating earlier access to physiotherapy and occupational therapy interventions-

'I think as things currently stand, so falls are a little bit of a hidden agenda. Within that, people with MS are further down the list and not getting referred. I just think that if there is some way, they are already out there living with the condition, and managing their falls and trips and slips and everything so is there a way they could be targeted as a population independent of their healthcare provider.' (Participant 4)

When asked about barriers to implementing falls prevention interventions time was mentioned by 10 of the participants and equipment was mentioned by 5 participants-

'Time [laughs] is the first one anyway, just with our caseload, sharing the gym space at the same time as well, so we don't always have all the equipment that you want available at that time.' (Participant 10)

'So we should have, and unfortunately in MS Ireland, we also don't have enough equipment to run those kind of programmes because we don't have even steps or stairs you know things like that.' (Participant 2)

This emphasises the fact that a practical falls risk screening tool that would be translatable for everyday use in clinical practise needs to be easy to administer, quick to carry out and involve low cost equipment.

Discussion:

This study used three data sources to explore what additional variables might further explain the variance in the falls prediction model. From data source A, the narrative literature review, essentially results are inconclusive due to poor methodological standards with no new predictor variable (as history of a fall is already included in the model) demonstrating an AUC value of greater than 0.7, sensitivity of greater than 80% and an odds ratio of greater than 1.0. Variables that do display any of these properties in isolation tend to have the value reported from one study cohort only. The information from data source B, the falls diaries, highlights the high rate of falls in this cohort, with more than half of fallers suffering injurious falls and 80% of those who suffered a relapse during the study period also reporting falls. This may indicate that full multi-disciplinary management is required at time of relapse and falls prevention interventions should be offered post relapse if indicated. The causes of falling listed are in line with the variables examined in the literature review and the location and timing of falls is important and may be relevant when considering falls risk assessment setting. The findings from data source C, the clinician interviews are in line with the

literature review also as common themes discussed are similar to some of the predictor variables examined including leg weakness, balance, cognition and dual task cost.

From the results of the literature review it is reassuring to see that it confirms the findings in relation to falls history as history of a fall in the past year was one of only two variables to have an AUC value ≥ 0.7 and a sensitivity $\geq 80\%$ (Cameron *et al.* 2013b). The other variable was the Berg balance scale but it did not have sensitivity and discrimination reported from the one study cohort and had a conflicting sensitivity of 32% reported in a different cohort (Prosperini *et al.* 2013). The poor predictive ability of clinical measures of balance for identifying falls risk in MS was previously highlighted in the systematic review earlier in this thesis (chapter two).

Our findings in relation to the importance of bladder issues and asking the person with MS about the presence of bladder dysfunction are similarly confirmed. It is evident from the literature review here that the presence of urinary incontinence with urgency has good discrimination (AUC = 0.82) and a very high odds ratio of 57.57 (Zelaya *et al.* 2017). Of the other variables with acceptable discrimination of ≥ 0.7 those with the highest discrimination include the ABC scale (0.92), the MSWS12 (0.91) and the FESI (0.89) (Tajali *et al.* 2017). This would indicate that to improve the accuracy of our falls risk model a self-report measure that examines balance confidence or fear of falls may be warranted. However, all of these measures demonstrated this high discrimination in one study cohort (Tajali *et al.* 2017) (n=84) only which was mainly relapse remitting MS with a younger mean age and shorter disease duration than other studies examining falls risk prediction (Nilsagård *et al.* 2009b; Gunn *et al.* 2013) meaning results may

not be applicable in all disease sub types and in older cohorts. It may be possible that two different falls risk models are required; one for younger people with milder disease status and a different one for older, more progressive cohorts.

A simple clinical assessment that might improve the accuracy of our model is the Ashworth scale for spasticity as it demonstrated reasonable discrimination with an AUC value of 0.73 for a model including this variable (Gunn *et al.* 2013) whereas for the development of our falls risk tool we only asked a simple yes/no question about presence of spasticity. However, sensitivity of Gunn *et al.*'s model was not greater than 80% and another study using the Ashworth scale demonstrated a low sensitivity of 58% (Nilsagård *et al.* 2009b). Comparison between studies is difficult due to wide heterogeneity in methodology with different fall definitions, different faller classifications and different durations of prospective monitoring. These studies did use the same monitoring period of 3 months but had different fall definitions and different faller classifications. Until reporting standards improve with specific protocols followed it is difficult to truly determine which variable is most sensitive or reliable to use for falls prediction.

Other clinical variables that possibly should be examined in more detail in a falls risk assessment tool include balance, lower limb weakness and fatigue. Balance and lower limb weakness were both frequently mentioned in the clinicians' interviews and all three of those predictors were found to be the most common cause of falls in the data from the falls diaries. From the literature review we know that to improve the accuracy of our falls risk tool we could include a more objective measure of balance using

instrumented data (Prosperini *et al.* 2013), a more objective measure of leg weakness e.g. using the Biodex system (Kasser *et al.* 2011) and a more detailed assessment of fatigue such as the Modified Fatigue Impact scale that has been shown to have good discriminative ability in previous research (Tajali *et al.* 2017). However, high tech equipment such as force plate posturography and Biodex systems are not going to be readily available in the usual healthcare setting in this country and therefore are not practical to include as components of a falls risk tool. A simple clinical measure of balance or mobility may be more feasible for use in an everyday clinic setting.

The type of clinical measure used to assess balance and gait is important and we now know from the narrative literature review and our paper in chapter three that the TUG did not demonstrate good discriminative ability or sensitivity for identifying falls risk and was not referenced by any of the clinicians in the interview data, indeed recent research has suggested the TUG is more reliable as a functional measure of mobility rather than an actual assessment of balance (Sebastião *et al.* 2016). From the results of the literature review the T25FW seems to have the greatest discriminative ability reported from multiple study cohorts and is recommended for use in clinical trials and to monitor disability progression as part of the MS functional composite measure (Fischer *et al.* 1999; Rudick *et al.* 2001). However, it looks at straight line walking only in a single task domain and does not measure balance dimensions in any detail. From this narrative review there does not appear to be any clinical measure of balance with appropriate levels of clinical utility and discriminative ability for identifying falls risk in MS.

Cognition measured with the Symbol Digit Modalities test (SDMT), was not statistically significant between fallers and non-fallers and was therefore not suitable for inclusion in the original model, and the literature review here agrees with our findings as it was not a predictor variable shown to demonstrate good levels of discrimination or high sensitivity for identifying falls risk. It may be argued that a different measure of cognitive impairment might be more appropriate than the SDMT but the SDMT has been shown to be more valid and reliable than the Paced Auditory Serial Attention Test (Sonder *et al.* 2014) and measures information processing speed and working memory that are the main domains involved in the type of cognitive impairment seen in people with MS (Parmenter *et al.* 2007). Possibly cognitive impairment as demonstrated in relation to dual task cost is a more relevant variable when considering falls risk.

The findings in relation to the location and timing of the fall is similar to other falls research in MS (Nilsagård *et al.* 2009b; Gunn *et al.* 2014), as are the findings in relation to the common causes of falls (Nilsagård *et al.* 2009a; Gunn *et al.* 2014). These studies and our data highlight the importance of timing of the assessment and location of the assessment. Ecological validity (Wegener and Blankenship 2007), a construct more commonly discussed in the behavioural sciences, is recently being examined more in relation to mobility assessment in MS and in particular walking capacity assessments. Recent research has demonstrated poor ecological validity for short walking tests such as the 10 metre walk test (Stellmann *et al.* 2015) and it is known that there is great variability day to day in mobility function for people with MS which limits the sensitivity of performance measures currently in use (Feys *et al.* 2012). Treating clinicians need to ask people with MS more detail about fall

characteristics such as rate of falls, presence of any injuries, location and time of falls. Potentially for a falls risk assessment to be most reliable and sensitive it should be carried out in the person's own home at the time of day when they have had previous falls or mobility limitations.

Conclusion:

From this analysis of three sources of data, it is suggested that the most appropriate additional variables for future studies identifying falls risk at a screening stage are a self-report question about bladder function (specifically urinary urgency with incontinence) and a measure of balance confidence such as the ABC or FESI. None of the clinical measures of balance demonstrate high levels of discriminative ability or clinical utility in more than one study and thus cannot be recommended. While more detailed objective measures such as the PPA or force plate posturography may be useful in a laboratory setting they are not readily available in primary care or tertiary centres and thus are not a realistic option in the current health care context of this country. Setting and timing of the falls risk assessment is also important and may provide more useful information if carried out in the person's own home at a time of day when previous falls have occurred.

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Chapter 7:

Discussion

Introduction:

This discussion chapter will firstly summarise key findings from each chapter of the thesis and will then explore the clinical and research implications of these findings. It will discuss methodological issues including faller classification, length of prospective falls monitoring, standardisation of dual task assessment and specific limitations of the thesis including sample size and recruitment bias. Methodological considerations for future studies will be examined as will considerations for research including public and patient involvement, model validation and implementation and considerations for clinical practice including treatment prioritisation. Throughout the chapter key learning points and reflection on potential changes and methods for improvement will be explored.

Key Findings of the Thesis:

Chapter 2-

The results of the systematic review show that currently no clinical measure of balance used with people with MS has sufficient levels of clinical utility or discrimination to be recommended to use to identify falls risk, but reporting standards are poor and methodological heterogeneity make true comparisons difficult. Some of the most common measures reported in the systematic review (chapter 2) include the Berg Balance Scale (BBS), the Timed Up and Go (TUG), the Falls Efficacy Scale International (FESI) and the Activities-specific Balance Confidence Scale (ABC)(Quinn *et al.* 2017). While these measures do show differences between fallers and non-fallers, this is mainly in studies using retrospective recall to establish falls

status and discriminative ability is commonly not reported. Retrospective recall is not the optimal method for reporting fall prevalence as previous studies of falls in people with MS have reported discrepancies between reported fall prevalence using retrospective recall and fall incidence using prospective diaries (Nilsagård *et al.* 2009; Dibble *et al.* 2013; Gunn *et al.* 2013a). This is not surprising considering the high prevalence of cognitive dysfunction in people with MS (Benedict and Zivadinov 2011). From measures that did have levels of discrimination reported, the ABC scale had the highest area under the receiving operating characteristic curve (AUC) value (0.92) but studies did not report sensitivity or specificity values, and the BBS had a high sensitivity value reported in one study (Nilsagård *et al.* 2009) but a contrasting value of 32% reported in a second study (Prosperini *et al.* 2013). As the TUG is significantly different between fallers and non-fallers in studies using retrospective falls recall, is commonly used and is quick and easy to carry out it warranted further investigation in a study using prospective monitoring of falls.

Chapter 3-

Chapter 3 describes that further investigation of the TUG through exploration of the discriminative ability and clinical utility of the TUG and TUG-Cognitive in people with MS where falls status was established with prospective diaries. Results suggest that it should not be used as a stand-alone measure for identifying falls risk. Both forms of the measure have an AUC value of less than 0.7 and while sensitivity scores are reasonable (82% and 77%) specificity values are low (34% and 30%) (Quinn *et al.* 2018). This is the first prospective study to report both values of discrimination and of clinical utility for the TUG in people with MS and the low AUC value demonstrated

is similar to that seen in other populations such as older people (Kojima *et al.* 2015) and people with Parkinson's disease (Kerr *et al.* 2010). For the TUG's sensitivity and discriminative ability to be improved it may need to be more objectively quantified, e.g. using body worn motion sensors and more accurate ways of objectively measuring balance will be discussed in a later section of this chapter.

Chapter 4-

While the TUG and TUG-Cognitive alone are not sensitive enough to reliably identify falls risk, another useful variable that is gaining increasing interest from researchers is dual task cost (DTC) and cognitive-motor interference (CMI). Motor impairment and cognitive dysfunction are two of the most common symptoms in MS (McDonald and Compston 2006), and have both been identified as falls risk factors in a previous systematic review (Gunn *et al.* 2013b). While CMI is known to be common in this condition (Leone *et al.* 2015) there is a scarcity of prospective studies examining the role of CMI and DTC and its association to falls in people with MS. In chapter 4, the results of an analysis on objective DTC and subjective problems with dual task activities demonstrated no significant difference for objectively measured DTC between fallers and non-fallers, but those who subjectively reported difficulty doing two things at once had a 2-fold increased risk of falling with a RR of 2.07 (95% CI 1.15, 3.71).

In addition to analysis of DTC in the paper that constitutes chapter 4 of this thesis, six different patterns of CMI were identified and the risk of falling was greatest for those

using pattern no.6 (changes in gait, numbers correct, $RR = 1.82$), suggesting that walking performance deteriorates at the expense of prioritising the cognitive task. Patterns of CMI have previously been reported in people post stroke and found to be similar for fallers and non-fallers in retrospective study designs (Plummer *et al.* 2013), but this is the first prospective study to report on patterns of CMI seen in people with MS. Awareness of specific CMI patterns may have implications for treatment regarding educating the individual so as to increase efficiency of their gait pattern and minimise falls risk. However, the type of CMI patterns demonstrated might have been more objectively established using video analysis and discussion from a team of experts and these patterns need to be further validated in a larger cohort. Previous analysis of gait during dual task conditions has involved analysis of spatial-temporal parameters in specific MS subtypes (Learmonth *et al.* 2014; Dujmovic *et al.* 2017) but this type of analysis is not possible outside of a laboratory setting and therefore does not translate well to clinical practice.

Chapter 5-

To derive a simple, low-tech procedure that would translate well to everyday practice was an important objective for the main falls risk model development study (chapter 5). After analysing various subjective and objective variables, the model with the greatest sensitivity (88%) and predictive validity ($AUC = 0.72$, 95% CI 0.62-0.82) included the variables of history of a fall, no visual problems, problems with bladder control and a slower speed on the Timed Up and Go. This model's sensitivity and discriminative ability values compare favourably with earlier models developed for use in MS (Kasser *et al.* 2011; Gunn *et al.* 2013a; Hoang *et al.* 2014) and unlike those

earlier models does not require any expensive specialist equipment or training. However, the specificity and amount of variance explained by this model is low and indicates that other factors not considered in our data set could potentially affect falls risk and should be examined in future research. The fact that the specificity is low means that some non-fallers may be referred for in demand resources that they do not actually need, but in a falls risk screening tool it is more important to have a high sensitivity and definitely identify the potential fallers, as it would cause more harm to miss potential fallers than to provide an intervention to non-fallers that may actually benefit from the intervention also.

Chapter 6-

Other potential falls risk variables that warrant further investigation were discussed in chapter 6 of this thesis, where three data sources (a narrative literature review, data from prospective falls diaries and a content analysis from clinicians' interviews) were used to explore other variables that might be added to future studies to further explain the variance of the model. The findings from those data sources demonstrate that to improve the sensitivity of our model it may be useful to include a self-report question specifically about bladder urgency rather than just asking about general bladder issues and a self-report measure in relation to balance confidence (e.g. the ABC scale or FESI). From the literature review it was evident that no predictor variable demonstrated an AUC value of greater than 0.7, sensitivity of greater than 80% and an odds ratio of greater than 1.0 in a single study cohort. From the falls diaries the high rate of falls and injurious falls was highlighted, causes of falls were in line with the variables from the literature review, location and timing of fall may be important.

Themes evident in data from the clinicians' interviews were similar to variables reported in the literature review and the importance of ecological validity in relation to assessment became evident. Timing and location of assessment is important and needs to be considered by the clinician when using a falls risk tool of this type.

In summary, the key findings of the results in the thesis were:

- 1) No clinical measure of balance currently in use is suitable to identify falls risk in MS.
- 2) The TUG and TUG-Cognitive should not be used in isolation to assess falls risk.
- 3) A self-report measure of difficulty dual tasking may be useful to identify fallers.
- 4) A model including the variables of no visual problems, problems with bladder control, history of a previous fall and a slower speed on the TUG demonstrates reasonably good sensitivity and discriminative ability for identifying fallers in MS but has poor specificity and explains 20% of the model variance.
- 5) To improve the amount of variance explained by the model it may be useful to add a question specifically about bladder urgency rather than general bladder issues and to incorporate a measure of balance confidence or fear of falls such as the ABC scale or FESI.

Considerations for Clinical Practice:

General Clinical Implications-

One of the most significant findings from this thesis is the high rate of falls among people with MS. From the prospective cohort study, a total of 791 falls were recorded from 56 participants, of which 34 were recurrent fallers who reported 2 or more falls during the 3-month study period. This high rate of falls may serve to increase the risk of other adverse outcomes including injuries, decreased confidence, lower levels of participation and an overall decrease in quality of life (Peterson *et al.* 2007; Peterson *et al.* 2008; Coote *et al.* 2013). Clinicians need to consider falls risk when treating people with MS and need to carry out comprehensive falls risk screening from an early stage of the disease; to help identify the level of risk sooner and refer for falls prevention interventions earlier when they can be of most benefit.

From the findings of this thesis it is clear that all health care professionals in contact with people with MS need to regularly ask about history of falls, the number of falls and injurious falls. They also need to enquire about specific problems with bladder urgency, determine if any visual problems are present and ascertain if the person reports problems doing two things at once. In combination with those self-report measures an assessment of gait speed using the TUG may be useful and will help the clinician to determine the individual's fall risk profile and to monitor changes over time. It is important for clinicians to be aware of the multifactorial nature of falls and not to rely on the use of one measure in isolation when assessing falls risk. Ecological validity is also relevant when assessing balance and mobility in people with MS and

clinicians must consider the wide variability day to day in level of function and symptom presentation when considering the setting and timing of their assessment.

As discussed in chapter 6 when exploring the variance of the falls risk model, biopsychosocial factors such as fear of falls are important and need to be considered in the context of falls risk assessment. A person's thoughts, emotions and behaviours may have a large impact on the type of coping mechanism they use to manage their symptoms and to minimise their falls risk; and indeed, the response and carryover they demonstrate in relation to falls prevention interventions. Social factors including economic, environmental and cultural aspects may also be important and this was not an area that was fully explored in the cohort study in this thesis. When designing the protocol for this study, the type of data collection tool utilised was based more so on the ICF framework with an emphasis on body functioning and structures and activities with balance, mobility and specific physical symptoms explored. Data exploring the person's level of participation and other environmental and social factors may have been useful and provided more insight into the individual's risk of falls in relation to their daily activities and quality of life. A falls risk assessment and intervention that incorporates biopsychosocial factors may have a more meaningful effect on the participation levels of the person with MS, and previous qualitative research has demonstrated that people with MS believe that improving participation-based outcomes are just as important as decreasing falls incidence when determining effectiveness of falls intervention trials (Gunn *et al.* 2017). The lack of biopsychosocial context is acknowledged as a limitation of the current model.

The Role of Prediction Tools in Treatment Prioritisation-

Clinical prediction models play an important role in healthcare by helping to calculate estimates of the likelihood of the occurrence of a particular patient outcome from multiple predictor variables and can help clinicians to make individualised diagnostic and therapeutic decisions (Steyerberg and Vergouwe 2014; Han *et al.* 2016). In chapter 5 the development of the falls risk model was reported, and results were discussed in terms of discriminative ability and clinical utility. While that chapter reported the sensitivity and predictive validity of the model as a falls risk screening tool, it did not explore how the model may be potentially used to help prioritise waiting lists and enable faster access to falls prevention interventions. Previous research has demonstrated limited access to physiotherapy services for those requiring neurological rehabilitation and an imbalance between increasing service demands and limited physiotherapy capacity (Adams *et al.* 2015). When service demand exceeds supply, prioritisation or triage systems are used to help clinicians to allocate their services appropriately and determine who needs to be seen first, how the service should be provided or indeed if treatment is required at all (Irion 1997; Gauthier *et al.* 2006). However, a systematic review of triage systems for allied health services found a paucity of evidence in relation to this topic and concluded that reliability may be improved if objective priority tools are used rather than relying on clinician judgement which may be quite subjective in nature (Harding *et al.* 2009).

In the Irish context there is limited formal information available in relation to prioritisation criteria, with many hospital outpatient clinics and primary care centres devising their own triage systems based on resource capacity and service

demands/needs. Members of the MS Society of Ireland reported access to physiotherapy services as their greatest unmet need in a 2005 market research survey. Similarly in the UK, a survey of people with MS demonstrated that advice about exercise was the most requested information source (Somerset *et al.* 2001) and that lack of information about physiotherapy services and excessive waiting list times was one of the most negative aspects of their overall management (Markwick *et al.* 2014). In a profiling study of physiotherapy services for people with MS in Ireland it was found that 47% of people with MS accessing physiotherapy used mobility aids and there was a short duration of physiotherapy received (mean of 3.6 hours) (Coote *et al.* 2010). This would indicate that people with MS are receiving far less than the 8-12 hours received by participants in studies that have demonstrated positive benefits of physiotherapy and exercise interventions (Cattaneo *et al.* 2007; Hoang *et al.* 2016b; Hugos *et al.* 2016). If a falls risk screening tool such as the one developed in this thesis was used to prioritise patients trying to access physiotherapy services such as a targeted falls prevention programme, they may receive a greater duration and more effective physiotherapy input, as such programmes tend to be 8 weeks or longer in duration.

The National Clinical Programme for Neurology (2016) recommends that people with MS have access to physiotherapy at all stages of the disease and that physiotherapy can play a role in monitoring disease progression, exercise prescription and advice regarding self-management (*National Clinical Programme for Neurology* 2016). Yet a recent survey of physiotherapists working on neurology services in primary care in Ireland showed that there are significant challenges and barriers to providing a quality service for people with neurological conditions in this country (McDaid *et al.* 2017),

that result in poorer patient outcomes and notable occupational stress for the clinician. A significant mismatch between their ideal service and the actual service provided was noted. A simple falls risk screening tool like the one developed in this study (chapter 5) may help to triage waiting lists more successfully and enable earlier access to falls prevention interventions for those at high risk. How the translation of this falls risk model to clinical practice may be facilitated will be discussed later in this chapter in the section on implementation of the model.

Considerations for Future Research:

Before contemplating model implementation or validation, the first consideration for future research should be revision of the falls risk model and incorporation of data that reflects the biopsychosocial aspects of falls risk. The model could be revised as suggested in chapter 6, by adding a measure of balance confidence and specifically asking about bladder urgency rather than general bladder issues, and then validating and implementing the revised model. Biopsychosocial data could be collected in the model revision study by changing the data collection tool (appendix 5.3) to incorporate questions about environmental and social factors including family support, home environment, education level and regular leisure pursuits. This may result in a more holistic falls risk model that explores more meaningful and important participation-based outcomes, which may have greater significance for the individual with MS.

Modifications to the Falls Risk Model -

Apart from more objective measures of mobility or balance using smartphone or accelerometer technology (as discussed in the later section on methodological considerations for future research), a further variable that could be added to the falls risk model is a self-report measure of balance confidence or fear of falls. These self-report measures link in with the biopsychosocial aspects of falls and add greater context to the impairment-based model in its current format. In chapter 6 both the ABC scale and FESI were commonly used self-report measures in falls risk studies and both had AUC values of ≥ 0.7 (Tajali *et al.* 2017). In addition, the FESI also demonstrated odds ratio values of ≥ 1 in multiple studies (Gunn *et al.* 2013a; Mazumder *et al.* 2015; Tajali *et al.* 2017). While a simple yes/no question about bladder control is included in the final falls risk model, it may be more sensitive to specifically ask about bladder urgency with incontinence as this demonstrated an odds ratio value of 57 in a recent prospective study (Zelaya *et al.* 2017).

Public and Patient Involvement (PPI)-

In relation to study design people with MS people should have been included from the initial stages of the cohort study as engagement of service users in research can lead to research of greater quality, impact and relevance (Chalmers 1995; Entwistle *et al.* 1998; Brett *et al.* 2014a). Public and patient involvement (PPI) is now considered a central component of the research process and results in the researcher developing a greater understanding and insight into their specialist area and service-users feeling empowered and more confident with greater control over their condition (Brett *et al.* 2014a; Brett *et al.* 2014b). PPI should have a much stronger focus in any model

revision and validation studies that would be carried out in the future. People with MS tend to readily engage with researchers and important information around falls risk and falls context has been obtained from previous qualitative analysis and interview methodologies (Peterson *et al.* 2007; Peterson *et al.* 2009; Carling *et al.* 2018). Thus, people with MS would be a useful resource in relation to the design of the falls screening questionnaire and the layout of the falls diaries in any future model revision or validation studies, to ensure the most appropriate and relevant information is collected. While different methods of engagement exist- focus groups, interviews, surveys, serving on a study board- the best method to achieve engagement has not been clarified and most studies use convenience sampling (Domecq *et al.* 2014). Ideally in a future model validation study focus groups and interviews with both service users and health care professionals could be utilised to ensure relevance of the variables being explored and to build relationships to aid knowledge translation and implementation at a later stage of the study.

Indeed building trust is one of the core principles of participatory research, along with finding a shared interest, power-sharing and building on existing strengths (Dalal *et al.* 2009). Empowering service users through a sense of responsibility is important in both research and general healthcare especially in chronic conditions such as MS that require lifelong therapy and greater healthcare utilisation (Rieckmann *et al.* 2015). The needs, wants and abilities of the people for whom an intervention or screening tool is targeted need to be considered and addressed and user (in the case of the falls risk screening tool both the clinician and the person with MS) perspective is important in the design and development of services (Hale *et al.* 2012). Involving health care professionals from an earlier stage of the falls model development study may have

provided greater insight into the usability of a falls risk screening tool of this type and indicated if it may be helpful in prioritising waiting lists and access to services, a topic which was explored earlier in the section regarding considerations for clinical practice. Involving clinicians and service users throughout the study phases may make dissemination and implementation of study findings easier and ensure the research findings translate well to everyday clinical practice. Implementation of the falls risk model could be carried out after model validation and impact analysis which will be discussed further in the following section.

Validation of the Falls Risk Model-

While many risk prediction models are developed and reported on in healthcare literature, very few are externally validated and actually used on a clinical basis, and when external validation is carried out it tends to demonstrate worse predictive performance (Siontis *et al.* 2015). In a recent paper examining how often newly developed risk prediction models undergo external validation, over 127 prediction models were examined and only 25% of those had external validation studies with AUC estimates significantly decreasing during external validation in comparison to the development study (Siontis *et al.* 2015). The predictive ability of a model often tends to be overestimated during the model development study, usually due to overfitting if the sample size is small and there are too few outcome events relative to the number of predictor variables (Moons *et al.* 2015). External validation involves applying the model to a new cohort of individuals that were not involved in the model development study and assessing its predictive performance. This can be done in several different ways; in temporal external validation individuals can be from the

same site as the development cohort but at a later time period, in geographical external validation participants are from a completely different institution or even country, and in domain validation new individuals are very different from the original individuals for which the model was first developed (Moons *et al.* 2012). To externally validate our falls risk model, temporal or geographical methods could be utilised, preferably using multiple recruitment sites across acute care and primary care settings. This would result in a larger sample size, which is required as a minimum of 100 events and 100 non-events are recommended for external validation studies (Vergouwe *et al.* 2005), and a more varied cohort than the original development study.

To the best of the author's knowledge none of the other models developed for assessing falls risk in MS (Kasser *et al.* 2011; Gunn *et al.* 2013a; Hoang *et al.* 2014) have been externally validated or had model impact analysis. Falls risk models developed for use in other cohorts have been externally validated to a certain extent but validation is not routinely reported. A recent systematic review of falls risk prediction models post stroke found only two studies reported any form of validation and none of the validated models demonstrated an acceptable performance (Walsh *et al.* 2016). A further study that externally validated two different falls risk prediction models in people post stroke found both models demonstrated poor predictive performance with AUC values of 0.56 and 0.55 (Walsh *et al.* 2017). A 3-step falls prediction model developed for people with Parkinson's disease (Paul *et al.* 2013) was externally validated in a prospective study and demonstrated comparable and acceptable discriminative ability to the development study with an AUC value of 0.74 (Lindholm *et al.* 2015). An external validation study of a falls risk tool for older people demonstrated good predictive ability in the validation cohort and also tested feasibility

of the tool by providing education and training to clinicians and having them complete an evaluation in relation to utility of the tool after a 3-month trial period (Tiedemann *et al.* 2010). This would be a worthwhile component to add to a future validation study of the falls risk model for people with MS and would demonstrate usability and applicability of the tool for those intended to use it. The next step after model validation would be impact analysis and model implementation (Keogh *et al.* 2014).

Impact Analysis-

Following model revision as discussed in the preceding paragraphs, model impact analysis and implementation could be carried out. Model impact studies are recommended after external validation to assess the impact on the change in behaviour of clinicians and also on cost effectiveness and on health outcomes (Moons *et al.* 2012). How frequently clinical prediction rules and models are used in clinical practice is unknown, and very few prediction models have undergone formal impact analysis to explore if they actually improve outcomes when used in clinical practice (McGinn *et al.* 2000). When considering prediction models the falls risk model in this thesis is currently level 1 evidence i.e. derivation of the prediction rule, but to be used in a variety of clinical settings with confidence regarding its sensitivity and effectiveness, it would need to be level 5 evidence i.e. broad impact analysis studies would have been carried out (Reilly and Evans 2006). When measuring the impact of a prediction model it is not enough to only include analysis of the traditional predictive values (e.g. sensitivity, specificity, AUC), but impact studies must also consider safety and efficiency (Reilly and Evans 2006). In this context safety is defined as the percentage of all individuals experiencing the predicted outcome who receive the targeted

intervention and efficiency is defined as the percentage of all individuals not experiencing the predicted outcome who do not receive the targeted intervention. This would indicate that falls prevention intervention programmes should be analysed in conjunction with use of the falls risk model to determine the appropriateness of the individuals receiving the targeted intervention.

Implementation of the Model-

Following model validation and impact analysis, implementation of the falls risk model involves dissemination of the research findings and practical approaches to implement the model and increase its use in a clinical setting. Some dissemination has already been carried out through poster and oral presentations at conferences, through presentations to the Neurology team in the recruiting hospital, to physiotherapy colleagues in the recruiting hospital, and to people with MS through updates in the MS Ireland research ezine. There are several different frameworks and models of implementation with the goal of knowledge transfer exchange. One of the best known frameworks is the Consolidated Framework for Implementation Research (CFIR) which recommends focusing on five domains to enhance implementation effectiveness (Damschroder *et al.* 2009)- the intervention, inner setting, outer setting, the individuals involved and the process for achieving implementation. Generally passive dissemination of information is not effective and to encourage implementation specific strategies are required such as educational outreach visits, interactive educational workshops, audit and feedback, use of local opinion leaders and multifaceted interventions (Bero *et al.* 1998; Boaz *et al.* 2011).

Another well-known framework is the PARiHS model (Promoting Action on Research Implementation in Health Services) which identifies three core elements necessary for successful implementation- the level and nature of the evidence, the context, and the process in which implementation is facilitated (Kitson *et al.* 1998). This framework is best used as a 2-stage process; a diagnostic and evaluative approach so that the intervention is shaped by key stakeholders for the specific situation in question, and that implementation is planned from the early stages of study design and considered at all stages of the study (Kitson *et al.* 2008). The task of trying to decide on an implementation framework to use can be daunting as there are over 60 models of implementation for knowledge transfer exchange (KTE) designed for various areas of health care (Prihodova *et al.* 2018). A recent review evaluated various models and highlighted 6 key components for successful implementation- the message, the stakeholders, the inner context, wider social context, cultural and economic context, and evaluation of the KTE process (Prihodova *et al.* 2018). The same research group involved in that review have now developed an Evidence-based Model for the Transfer and exchange of Research Knowledge (EMTReK) and they recommend a multifaceted strategy combining different approaches to achieve successful KTE (*EMTReK, an Evidence-based Model for the Transfer and exchange of Research Knowledge* 2017).

Following on from those recommendations, in order to achieve successful implementation of the falls risk model into clinical practice a multifaceted approach is required. The main message from the study must be highlighted and key stakeholders including Neurologists, MS nurse specialists, physiotherapy and occupational therapy managers and people with MS must all be involved in the implementation process. Ideally these stakeholders would be involved from the outset

(as discussed earlier in the section on PPI) and a relationship based on trust and shared interests would be established and help to facilitate knowledge transfer. The context and setting for dissemination should be considered and will involve different locations depending on the stakeholders involved. Those settings may include journal club meetings, interactive training sessions and patient workshops across the acute and primary care setting. Social media platforms also play a role in dissemination of research findings (Scanfeld *et al.* 2010; Keller *et al.* 2014) and previous research has demonstrated internet usage to be high among people with MS with many using online platforms to obtain health related information and to get peer support (Lejbkowitz *et al.* 2010). After carrying out strategies to encourage implementation, evaluation of KTE should be explored and this may be done through participant feedback and evaluation post workshops, through clinician and individual surveys and through service audit at a later date to evaluate any change in clinical practice. The model in its current state is not ready for validation, impact analysis or implementation and this is partly related to certain methodological issues that will be discussed in the following section.

Methodological Issues:

Faller Classification-

The most significant methodological issue, that comes to light firstly in the systematic review in chapter 2 but is applicable throughout the whole thesis, is the variability and lack of clarity relating to the definition and classification of a ‘faller’. The number of falls necessary during the monitoring period to classify a person as a faller remains unclear, and variability in different studies makes comparison and analysis of study

findings difficult. Some researchers examining falls risk in MS define a faller as a person with 1 or more falls (Coote *et al.* 2013; Nilsagård *et al.* 2016), others define it as the occurrence of 2 or more falls (Gunn *et al.* 2013a; Kalron and Allali 2017) and still others classify a faller as a person with 3 or more falls (Hoang *et al.* 2014). When looking in more detail at the reasoning behind why a particular faller definition is chosen the findings are contrasting in nature. Some studies don't give any justification for their choice of definition (Cameron *et al.* 2013b; Vister *et al.* 2017) and of those that do the reasoning referenced varies.

The definition of a faller as a person with 1 or more falls is recommended by the International MS Falls Prevention Research Network (IMSFPRN) as it only takes one fall to cause injury and related consequences such as fear of falling or activity curtailment (Coote *et al.* 2014) and some subsequent studies have based their faller definition on this recommendation (Tajali *et al.* 2017). Gunn *et al.* (Gunn *et al.* 2013a) based their definition (faller with 2 or more falls) on recommendations from the Prevention of Falls Network in Europe, ProFaNE (Lamb *et al.* 2005) but these recommendations for falls research in older people do not state fallers should always be classified as a person with 2 or more falls but rather that multiple categories should be explored and reported including fallers/non-fallers/frequent fallers. More recent studies (Kalron and Allali 2017; HersHKovitz *et al.* 2019) in falls risk in MS then went on to base their faller definition on the Gunn (2013a) study. Hoang *et al.* (2014) discuss the concept that greater than two falls are more likely to indicate physiological impairment and represent chronic conditions but the reference for this statement is based on falls in older people and is quite dated at this stage (Nevitt *et al.* 1989). That group then go on to define a faller as a person with 3 or more falls because of the high

prevalence of falls in MS with a prevalence greater than that seen in older people. The same reasoning of 2 falls being more indicative of physiological impairment and chronic disease based on the same cited study is used by Kasser *et al* (2011) but they do also report risk findings in relation to a faller being a person with 1 or more falls to allow for evaluation of all falls versus no falls.

This reporting of multiple faller categories is seen in other recent studies investigating falls risk in MS (Mazumder *et al.* 2015; Hoang *et al.* 2016a; Zelaya *et al.* 2017) and may possibly represent the optimal method for reporting faller data and provide the most transparent findings. Indeed, in the recommendations from the IMSFPRN they recommend using the term ‘multiple faller’ or ‘frequent faller’ for any participant with 2 or more falls and also propose reporting the number of falls per person per year as a primary outcome in falls research trials (Coote *et al.* 2014). Reporting of this computation is also recommended in the elderly (Lamb *et al.* 2005) and may help overcome issues of confusion and heterogeneity around faller classification categories. The IMSFPRN (Coote *et al.* 2014) recommend collecting data on injurious falls and on all type of injuries, not just those requiring medical attention, as many falls among people with MS are not reported to a healthcare professional (Matsuda *et al.* 2011) and minor injuries can still have a significant impact on the person in relation to time off work or psycho-social constructs such as fear of falls (Peterson *et al.* 2008). Previous research has shown the prevalence of injurious falls to be greater in people with MS than in healthy controls (Mazumder *et al.* 2014) with varying prevalence rates of 34% (Matsuda *et al.* 2011) to 58% (Hoang *et al.* 2014) reported across studies. The injury rates in this longitudinal study were lower than previously reported findings, with 33% of participants reporting injurious falls (only 3% accessed medical services for

injuries) over the 3-month monitoring period and thus injurious falls was not deemed a significant faller classification to base the falls risk model analyses on. The different levels of significance assigned to all fallers (person with 1 or more falls), multiple fallers (person with 2 or more falls) and injurious fallers will be discussed further in a later section of this chapter in relation to treatment prioritisation.

Length of Prospective Falls Monitoring-

The monitoring period for collecting data on falls events varies considerably between studies with some researchers collecting data using falls diaries for a three-month period (Nilsagård *et al.* 2009; Gunn *et al.* 2013a; Prosperini *et al.* 2013; Hoang *et al.* 2016a; Zelaya *et al.* 2017) and others for longer periods of up to 6 months (Cameron *et al.* 2013b; Mazumder *et al.* 2015; Etemadi 2016; Tajali *et al.* 2017; Vister *et al.* 2017) or even a year (Dibble *et al.* 2013; Kasser *et al.* 2014). Six and three-month follow up periods tend to be both commonly reported, whereas a 12 month follow up is less frequent. Even within different studies from the same researcher discrepancies arise with research groups using three months in one study (Cameron *et al.* 2013a; Hoang *et al.* 2016a) and then the same group using 6 months in a different study (Cameron *et al.* 2013b; Hoang *et al.* 2014).

Of the studies to date in MS using prospective monitoring of falls only four of them reference or explain their reasoning for choosing a specific monitoring period. Two studies (Hoang *et al.* 2014; Tijjsma *et al.* 2017) base their choice on the recommendations for falls prevention trials in older people (Lamb *et al.* 2005), but the

ProFaNE recommendations do not actually specify a length of time for falls monitoring but rather advise a minimum of monthly reporting with a 12 month period recommended for falls intervention studies that may have a delayed effect and require a longer follow up time point to demonstrate evidence of effect. Cameron et al (2013a) base their method on a cross-sectional study that doesn't actually mention prospective falls monitoring periods at all (Finlayson *et al.* 2006).

Another reference cited in relation to falls monitoring was Perry et al (2012) who examined the correct completion and return rate of falls diaries in a cohort of older adults. They found that 60% of diaries returned over a 6-month monitoring period were correctly completed and that those at a higher risk of falling (as measured using the Falls Risk Assessment Tool, FRAT) were both less likely to return diaries and more likely to report falls. This may indicate that a certain proportion of fallers are missed when using falls diaries to monitor falls rate. However, this was not an issue with our falls risk model study as there was a falls diary return rate of 99.7% and telephone follow-up was utilised to clarify any missing data from diaries and to confirm any unusual findings reported (chapter 5).

When deciding the reporting period for falls diaries it is important to have a balance between accurate data collection and burden or inconvenience for the study participant. The reporting period needs to be long enough to capture an accurate representation of falls rates but short enough to avoid placing an excessive burden on the study participant. As the prevalence of falls in MS is greater than that seen in older people (Campbell *et al.* 1990), the International MS Falls Prevention Research

Network (IMSFPRN) recommends a three-month monitoring period in MS falls related trials (Coote *et al.* 2014) but advise the aim of the intervention must also be considered when deciding on a follow up time point. While the optimal time period for falls monitoring has not been reported in either older adults or in MS (Ganz *et al.* 2005; Matsuda *et al.* 2011), it is widely accepted and agreed upon that prospective falls monitoring is more reliable than retrospective recall and that a minimum of monthly reporting with telephone or face to face interview should be used to clarify any missing data (Lamb *et al.* 2005; Hannan *et al.* 2010; Coote *et al.* 2014). If the computation of number of falls per person per year is reported (as discussed earlier in the faller classification section), then the length of prospective monitoring chosen is not so relevant and comparison of results from different studies is easier.

Standardisation of Dual Task Assessment-

Similar to variety in faller classification and falls monitoring periods, significant variation is also present in the methods used to assess an important variable related to falls risk; dual task cost (DTC). There is a growing body of evidence exploring the role of DTC and cognitive motor interference in people with MS but recent reviews suggest methodological limitations make comparison of results difficult, and highlight the need for a standardised dual task assessment that measures the DTC of both the motor and cognitive task and that gives clear instructions regarding task prioritization and speed selection (Leone *et al.* 2015; Postigo-Alonso *et al.* 2018). A form of gait assessment is the most common motor task reported, some analysing spatial temporal parameters using the GAITRite walkway (Kalron *et al.* 2010; Learmonth *et al.* 2014; Motl *et al.* 2014) while others use more traditional timed tests including the 10 metre

walk test (Gunn *et al.* 2013a) and the timed 25 foot walk (Tajali *et al.* 2017). The DTC of cognition is commonly not reported but is gaining increasing attention with recent studies highlighting a worsening of cognitive performance under dual task conditions (Downer *et al.* 2016; Etemadi 2016). A variety of cognitive tasks have been utilised including word list generation (Sosnoff *et al.* 2011; Wajda *et al.* 2013) and various counting tasks such as counting backwards in serial 3s or serial 7s (Gunn *et al.* 2013a; Kirkland *et al.* 2015) or pre-recorded digit-span sequences (Butchard-MacDonald *et al.* 2017). Interestingly that latter study is the only study, apart from our analysis reported in chapter 4, that uses a form of subjective assessment of dual task cost where they used a 10-item Dual Tasking Questionnaire. However no significant correlation was found between the self-report measure of dual tasking ability and decrement scores of objectively measured balance task performance under dual task conditions (Butchard-MacDonald *et al.* 2017). As there was no measure of falls rate in that study it is impossible to draw conclusions about findings from the self-report measure of dual tasking ability and association to falls risk.

Studies that examined objectively measured DTC in relation to falls risk demonstrate conflicting results (Gunn *et al.* 2013a; Wajda *et al.* 2013; Etemadi 2016). In a cross sectional study Wajda *et al.* (2013) found a significant correlation between falls risk (measured using the Physiological Profile Assessment) and dual task cost of walking, and the same group in a later study reported a significant association between the DTC of cognition and balance confidence, measured with the Activities-specific Balance Confidence Scale (Wajda *et al.* 2016) which is a measure known to be predictive of future falls risk (Tajali *et al.* 2017). This may indicate that the dual task of cognition

is associated with falls risk and this variable has been assessed in recent studies using prospective diaries for falls monitoring, as explained in the following paragraph.

In studies using prospective diaries for falls monitoring conflicting results have been reported regarding DTC with some researchers finding no significant difference between fallers and non-fallers in relation to the DTC of the motor task (Gunn *et al.* 2013a; Tajali *et al.* 2017) assessed using timed walks, whereas a study that used the Timed Up and Go Cognitive did find it was predictive of falls (Nilsagård *et al.* 2009) and a recent study found the DTC of cognition was related to recurrent falls risk (Etemadi 2016). When assessing DTC the cognitive task chosen is important and must represent a significant cognitive load to actually cause cognitive motor interference (CMI) (Srygley *et al.* 2009). The cognitive task utilised when assessing DTC represents a limitation of our analysis of DTC and its association to falls (chapter 4). The cognitive task used involved counting backwards in serial threes and may not have constituted a large enough cognitive load to truly cause significant CMI. The dual task of cognition should also have been measured as this variable has been shown to be associated with falls (Etemadi 2016) and both motor and cognitive DTC needs to be assessed to determine which task the individual is prioritising and how that choice may affect their mobility. Previous research in Parkinson's disease demonstrated that people with Parkinson's prioritise the cognitive task to the detriment of their walking performance (Bloem *et al.* 2006) and this has also been reported in studies of people with MS even when instructions have been given to give equal attention to both tasks (Allali *et al.* 2014). A recent systematic review (Postigo-Alonso *et al.* 2018) recommended that verbal fluency is the most sensitive cognitive task to use when assessing CMI in people with MS, as it has a greater cognitive load than counting tasks

and depends on frontal and temporal lobe processes that are commonly impaired in people with MS and that share neural networks with those involved in gait control (Gazzaley and D'Esposito 2006; Yogev *et al.* 2008). Apart from the assessment of DTC, further limitations of this thesis will be discussed in the following section.

Limitations of the Thesis:

Sample Size-

On reflection, certain methodological factors regarding the main longitudinal study (chapter 5) may be considered as limitations. The sample size for model development was not considered at the protocol stage but rather the sample size of 100 was chosen based on previous falls research in MS (Prosperini *et al.* 2013; Kasser *et al.* 2014) and was considered a feasible and realistic recruitment target for a single site study. As the sample size was calculated post hoc this represents a limitation of the study. In recommendations regarding sample size calculation for risk prediction model development studies, there is a lack of clarity. If the number of predictor variables is much greater than the number of outcome events (in this instance fallers), there is a risk of overestimating/overfitting the predictive ability of the model in question (Han *et al.* 2016). Many go by the rule of thumb of 10 events per variable i.e. at least 10 events (in this study fallers) per predictor variable (Peduzzi *et al.* 1995), but others think that rule is too strict (Vittinghoff and McCulloch 2007) especially if adequate control of confounding has been undertaken.

The sample size used directly affects the choice of statistical analysis methods suitable for use and meant that it was possible to do regression analysis based on a faller classification as a person with 1 or more falls only. As there were 56 fallers with 1 or more falls (chapter 5) this classification was chosen to allow model development with a potential of 5 variables as a minimum of 10 events is usually recommended per variable (Ogundimu *et al.* 2016). Ideally analysis for both faller and multiple faller (person with 2 or more falls) classifications would be carried out and reported on as recommended by the IMSFPRN (Coote *et al.* 2014), however the multiple faller classification would have resulted in 34 fallers which would limit the potential number of predictor variables to three. The issue of faller classification is complex (as discussed earlier in the first section about general methodological issues) but is a concept that needs consideration from the start of study design and will affect the choice of analysis method and may alter the significance of results. To make comparisons of results from different studies easier, large sample sizes should be used to allow analysis of both faller and multiple faller classifications that would facilitate reporting in the format recommended by both the IMSFPRN (Coote *et al.* 2014) and ProFaNE (Lamb *et al.* 2005).

A further limitation of this thesis is that multiple uses of data and various forms of data analyses were carried out on data collected from the same sample. Ideally the different analyses explored for each chapter would have been done using data from different cohorts, but realistically considering the time frame for the overall thesis and the length of time required for participant recruitment and data collection this was not possible.

Recruitment Bias-

There was also potentially a recruitment bias in this study; the role of screening for study eligibility fell to the treating doctor or nurse specialist in clinic and they may have only considered the falls risk study when assessing more progressive patients. This would partly explain the large predominance of secondary progressive MS in the study cohort but is also related to the inclusion criteria which stated participants must have an EDSS level of 3-6.5 which would exclude less impaired people with the relapse-remitting sub type. If the principal investigator was present at the screening stage, there may have been a wider range of MS subtypes and mobility levels recruited that would have improved the applicability of the model to the general MS population. Unfortunately, due to the recruitment setting being a busy outpatient clinic based in a large tertiary hospital this was not logistically possible. Potential changes to the recruitment process to improve the generalisability of the model and help external validity will be discussed in following sections.

Methodological Considerations for Future Studies:*Increase the Sample Size-*

Following on from the discussion on study limitations above the first consideration is the need for a larger sample size. If a larger study cohort were recruited from multiple sites (e.g. acute care, primary care, patient organisations), it would potentially result in a wider variety of MS sub types, age range and mobility levels and would improve the applicability of the model for a wider MS context. A larger sample size would also enable more detailed analysis of both faller and multiple faller classifications and

would allow reporting of results in line with recommendations from international falls research networks (Lamb *et al.* 2005; Coote *et al.* 2014). This would strengthen the significance and robustness of our study findings and allow more comparison with other studies on falls risk in MS that reported results based on multiple faller classifications (Kasser *et al.* 2011; Mazumder *et al.* 2015; Zelaya *et al.* 2017).

Change of Balance Measure-

Based on the findings regarding the discriminative ability and clinical utility of the TUG (chapter 3) (Quinn *et al.* 2018) it is now reasonable to state that it was not an appropriate measure of balance to use in a falls model development study. However, at the time of study design it was chosen as it has good face validity for assessing falls risk involving turning and mobility transitions that are commonly associated with falls in people with MS (Gunn *et al.* 2014) and is recommended for use in both research settings and clinical practice by the American Physical Therapy Association Evidence Database to Guide Effectiveness Task Force (Potter *et al.* 2014). Furthermore, the TUG has been shown to be associated with global cognitive function and executive function in older adults (Herman *et al.* 2011; Donoghue *et al.* 2012) and in people with MS (Allali *et al.* 2012). The TUG and TUG Cognitive require no specialist equipment or training and the TUG Cognitive had been shown to be associated with falls risk in MS in a previous longitudinal study (Nilsagård *et al.* 2009). However, more recent prospective studies have shown it does not demonstrate significant discriminative ability or good predictive validity for identifying future falls risk in people with MS (Tajali *et al.* 2017; Quinn *et al.* 2018) and may be more appropriate as a functional measure of mobility (Sebastião *et al.* 2016) and possibly to monitor disease

progression (Kalron *et al.* 2017). If used to assess falls risk some form of instrumented TUG using body worn sensors may be more appropriate and has been shown to be sensitive and reliable in MS (Craig *et al.* 2017; HersHKovitz *et al.* 2019) but further prospective studies of association with fall risk are required. Instrumented objective measures of balance such as the I-TUG and static posturography may be more sensitive for identifying falls risk (Mancini and Horak 2010; Prosperini *et al.* 2013) and if these systems became less expensive and more readily available outside of the laboratory setting they may be an option worth considering for clinicians working in the area of falls risk assessment and treatment. More objective and quantifiable methods of balance assessment will be discussed further in the following paragraphs.

Objective Measures of Balance and Smartphone Systems-

Body worn motion sensors are more readily available than laboratory based force platforms and are reasonably low cost and suitable for use in community and clinic settings (Shanahan *et al.* 2018). They have been previously used to monitor gait and balance impairment in people with MS (Moon *et al.* 2017; Sun *et al.* 2018). The instrumented TUG has been explored in MS cohorts and has been shown to be reliable, associated with disease stage and more sensitive than traditional timed tests alone (Spain *et al.* 2012; Greene *et al.* 2015). While it has not been examined in prospective studies evaluating falls risk in people with MS, it has been shown to be reliable for identifying falls risk when combined with clinical variables in a large cohort of older people (Greene *et al.* 2017) and a recent smaller study with 6 months of prospective falls monitoring showed promising results for identifying falls risk in people with Parkinson's disease (Greene *et al.* 2018).

While force platform systems that give measures of static and dynamic posturography are expensive and usually laboratory based they have been shown to be reliable in predicting falls (Kasser *et al.* 2011; Prosperini *et al.* 2013). A standardised objective measure of balance such as posturography has many advantages over simple clinical measures including decreased variability in test performance (both across raters and across multiple sites), decreased subjective nature of scoring and an increased sensitivity to even very small changes (Mancini and Horak 2010). The main drawback to these systems is the high cost to acquire the equipment and a need for specialist training for staff, but a recent review of force platform measures in MS suggested using a commercially available low-cost device such as the Nintendo balance board (Prosperini and Pozzilli 2013) and a study exploring its use for posturography analysis showed it can be successfully used to gain a wide range of measures (Severini *et al.* 2017). It has been used in previous pilot intervention trials in MS (Brichetto *et al.* 2013; Pau *et al.* 2015) and a recent randomised controlled trial found the Nintendo Wii Fit is comparable to traditional balance interventions (Robinson *et al.* 2015) but qualitative analysis exploring its usability recommend modifications to commercial games to improve its ability to accommodate different functional levels (Plow and Finlayson 2014).

A different form of technological adjunct that may have improved the strength of the falls model in terms of sensitivity and variance is a smartphone app using some form of built in motion sensor. Motion wearable devices including accelerometers, gyroscopes and pedometers can be embedded into smartphone apps and provide an unobtrusive method of monitoring and assessment that could provide the clinician with real time data over a period of days from a variety of different settings (Sparaco

et al. 2018). This form of falls monitoring would potentially have greater ecological validity than a clinic based assessment as most falls tend to occur in the person's own home during activities of daily living (Carling *et al.* 2018). However, certain limitations in relation to accelerometer devices must be highlighted- there can be many false positives as the accelerometer may not be able to distinguish real falls from activities such as sitting quickly or jumping (Li *et al.* 2009) and location of the device affects accuracy with devices usually recommended to be worn at the waist (Kangas *et al.* 2008). Much of the evidence pertaining to falls detection algorithms using accelerometers or gyroscopes has been explored in simulated falls situations and when studies do evaluate their systems on real falls data the sensitivity is much lower than what was demonstrated with the simulated falls (Bagala *et al.* 2012). To determine if these accelerometer devices are more reliable and superior for monitoring falls than traditional falls diaries, their performance in longitudinal studies with large sample sizes must be evaluated and compared to falls data collected from diaries for the same cohort over the same specified time period.

An advantage of smart phone technology with a built in accelerometer is that not only can it detect the fall, but it can also record location of the fall and report the fall to the system and user and caregiver via an alert system that typically involves an audible alarm, a text message or automatic voice call (Lee and Carlisle 2011). A recent review of smartphone based solutions for falls detection and prevention concluded that the quality of inbuilt sensors may not be adequate for accurate falls detection, there may be placement and usability issues and battery life can be a limitation (Habib *et al.* 2014). However, a customised app specifically designed for falls detection may be more accurate and it is known that there is a high level of smartphone usage among

people with MS in Ireland and they are amenable to using them for health related purposes (Griffin and Kehoe 2018). In the initial protocol for the falls model development study (chapter 5), one of the study aims was to test the feasibility and clinical utility of an Android phone app used during the TUG. Data on sway, acceleration and angle of sway were collected during the assessment phase via a specially designed smartphone app but unfortunately this data has not been analysed due to the withdrawal of a staff member from the Computer Engineering Department at UL who had initially been involved in the study. In future studies to refine this model and improve its predictive ability further this smartphone data may be a useful additional variable.

Conclusion:

In conclusion this thesis provides new and valuable information in relation to falls risk assessment in people with MS. It highlights the poor sensitivity of clinical measures of balance for identifying falls risk in isolation and recommends use of a multi variable model that includes self-report measures when screening for falls risk. In the section on methodological considerations possible ways to improve this model further are explored and these potential modifications should be applied before validating and implementing the model in clinical practice. For future studies on falls in MS it is important to clarify the variability around faller classification and length of falls monitoring. To overcome this limitation multiple faller categories should be explored and reported on using prospective falls monitoring for a minimum of 3 months, and the number of falls per person per year should be reported for all faller categories.

When examining dual task cost a standardised assessment should be utilised that carefully considers the cognitive task chosen and that gives clear instructions regarding task prioritisation.

To develop the findings from this thesis further the falls risk model could be revised to incorporate a self-report measure of balance confidence and other biopsychosocial aspects. The next step would be a validation study with a large sample size, recruited from multiple sites including acute care and primary care settings to allow for reporting of model sensitivity in relation to different faller classifications and to determine if the model is applicable to a more heterogeneous MS cohort with a wider range of EDSS levels and varying disease sub types. In the model revision and validation studies there should be public and patient involvement throughout as information from clinicians and service users will be invaluable in relation to usability and implementation of the model. If the falls risk model is successfully implemented, it could have a significant impact on clinical practice by identifying those at risk of falls earlier and by enabling earlier access to falls prevention interventions through better prioritisation systems. This could result in positive outcomes for the individual with the condition regarding increased confidence, greater participation and decreased number of falls, but would also potentially have a wider socioeconomic benefit resulting from decreased healthcare utilisation and increased work productivity.

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Appendices

Appendix 2.1: MOOSE Checklist for Meta-analyses of Observational Studies

Item No	Recommendation	Reported on Page No
<i>Reporting of background should include:</i>		
1	Problem definition	27
2	Hypothesis statement	28
3	Description of study outcome(s)	28
4	Type of exposure or intervention used	28
5	Type of study designs used	28
6	Study population	28
<i>Reporting of search strategy should include:</i>		
7	Qualifications of searchers (eg, librarians and investigators)	28
8	Search strategy, including time period included in the synthesis and key words	28 & appendix 2.2
9	Effort to include all available studies, including contact with authors	28
10	Databases and registries searched	28
11	Search software used, name and version, including special features used (eg, explosion)	28
12	Use of hand searching (eg, reference lists of obtained articles)	28
13	List of citations located and those excluded, including justification	N/A
14	Method of addressing articles published in languages other than English	N/A
15	Method of handling abstracts and unpublished studies	N/A
16	Description of any contact with authors	29
<i>Reporting of methods should include:</i>		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	29
18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	29
19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	29
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	N/A
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	30
22	Assessment of heterogeneity	30
23	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-	31

	response models, or cumulative meta-analysis) in sufficient detail to be replicated	
24	Provision of appropriate tables and graphics	Tables 2.1a and 2.1b pg 37, table 2.2 pg 40, Figures 2.1 pg 33
<i>Reporting of results should include:</i>		
25	Graphic summarizing individual study estimates and overall estimate	Figure 2.2, pg 42
26	Table giving descriptive information for each study included	Appendices 2.3 and 2.4
27	Results of sensitivity testing (eg, subgroup analysis)	N/A
28	Indication of statistical uncertainty of findings	43
<i>Reporting of discussion should include:</i>		
29	Quantitative assessment of bias (eg, publication bias)	N/A
30	Justification for exclusion (eg, exclusion of non-English language citations)	N/A
31	Assessment of quality of included studies	48
<i>Reporting of conclusions should include</i>		
32	Consideration of alternative explanations for observed results	46,47
33	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	48
34	Guidelines for future research	49
35	Disclosure of funding source	N/A

Appendix 2.2: Search Strategy

P = Population or Patient group: people with Multiple Sclerosis
I = Intervention: not applicable
C = Comparator: clinical measure of balance
O = Outcomes: method of falls reporting to classify as faller or non-faller
T = Time period: no limit to search

Other Limits

Types of Research (following evidence hierarchy)

- Cohort studies – with prospective falls monitoring
- Primary research – RCTs (baseline data)
- Primary research – cross sectional observational studies

Search dates

- No limit on start date - October 2017

Language

- No restriction

Sources

Published literature:

AMED,
 CINAHL,
 Medline (first three through EBSCO search platform),
 Scopus,
 PubMed Central.

Record sheet of searches

Database and Date Searched	Search Terms	Number Retrieved	Number of hits
Medline, date – 15/03/17	#1 Multiple Sclerosis #2 MS #3 Acute Fulminating Sclerosis #4 Disseminated #5 (#1 OR #2 OR #3 OR #4) #6 Balance #7 Postural control #8 Imbalance #9 Postural instability #10 Stability #11 (#6 OR #7 OR #8 OR #9 OR #10) #12 Fall* #13 Fall risk #14 (#12 OR #13) #15 (#5 AND #11 AND #14)	487 results	41 abstracts screened. 23 studies suitable for inclusion (3 RCTs, 4 prospective cohorts, 16 cross sectional)

Appendix 2.3: Descriptive characteristics of prospective cohort studies

Author, Year Study Design	Eligibility Criteria	Recruited	Assessment Measures of Falls and Balance	Faller Definition and Classification
Cameron et al, 2013 Prospective cohort	<p><i>Inclusion Criteria:</i></p> <ol style="list-style-type: none"> 1. Mild to moderate Multiple Sclerosis. 2. No clinically significant relapse in past 30 days. 3. Able to complete a written daily record of falls for 6 months. <p><i>Exclusion Criteria:</i></p> <ol style="list-style-type: none"> 1. Self-reported condition other than Multiple Sclerosis known to affect balance/gait. 2. Unable to follow instructions in English. 	<p>52 people with Multiple Sclerosis: 94% had relapse remitting form, Mean age 39.8 (8.4), Male: Female=17:35, Mean Disease Duration 6.3 (5.6), Mean Expanded Disability Status scale 2.8 (1.5), Faller: Non-faller = 37: 15</p>	<p>Falls record-prospective reporting using monthly fall calendars for 6 months, also retrospective recall for past 2 and 12 months. Activities-specific Balance Confidence Scale and Falls Efficacy Scale international.</p>	<p>Fall defined as an unexpected event that results in the person ending up on the ground, floor, or any lower surface.</p> <p>Faller = person with 1 or more falls.</p>

	<p>3. Unhealed fractures or other conditions that could cause injury during balance testing.</p> <p>4. Blindness</p> <p>5. Unable to walk more than 100 metres</p>				
<p>Dibble et al, 2013</p> <p>Prospective cohort</p>	<p><i>Inclusion Criteria:</i></p> <ol style="list-style-type: none"> 1. Able to walk 25 m independently without rest (with or without a mobility aid). 2. Willingness to complete balance examinations and to complete falls record for a 12-month period. <p><i>Exclusion Criteria:</i></p> <ol style="list-style-type: none"> 1. Other medical conditions that prevented their participation in the study. 2. Refusal to be contacted for phone follow up regarding falls events. 	<p>38 people with Multiple Sclerosis:</p> <p>Mean age of fallers 53.83 (9.67), mean age of non-fallers 53.26 (11),</p> <p>Expanded Disability Status Scale mean 4.74 (1.29) in fallers and 4.33 (2.0) in non-fallers.</p> <p>Disease duration in fallers group 14.0 (10.03), disease duration in non-fallers 14.37 (10.95).</p> <p>Fallers: Non-fallers = 23: 15</p>	<p>Prospective falls diary (over 12 months), retrospective falls recall (asked at end of 12-month period)</p> <p>Activities-specific Balance Confidence scale,</p> <p>Berg balance scale,</p> <p>Timed Up and Go,</p> <p>Dynamic Gait Index.</p>	<p>Fall defined as an event in which the individual unintentionally came to rest on the ground or a lower surface, not as the result of a major intrinsic event (e.g. heart attack) or an overwhelming extrinsic event (e.g. ice).</p> <p>Faller = person with 2 or more falls.</p>	

<p>Gunn et al, 2013</p> <p>Prospective cohort</p>	<p><i>Inclusion Criteria:</i></p> <ol style="list-style-type: none"> 1. Expanded Disability Status Scale score of between 3.5 and 6.5 (scored by telephone interview). <p><i>Exclusion criteria</i></p> <ol style="list-style-type: none"> 1. Unable to effectively give informed consent. 2. Co-morbidities that may significantly impact on balance. 	<p>148 people with Multiple Sclerosis: Mean age 57 (10), Male: Female= 34:114, Relapse remitting= 42, Secondary Progressive = 66, Primary progressive= 37, Benign= 2, Malignant= 1, Use of a walking aid, N= 110 Faller: Non- faller = 104: 44</p> <p>Expanded Disability Status Scale values reported in individual breakdown, no mean reported.</p>	<p>Prospective falls recall (falls diaries for 3 months post assessment), Falls Efficacy Scale International, Physiological Profile Assessment.</p>	<p>Fall defined as a slip or trip in which the person lost balance and landed on the floor or ground or lower level.</p> <p>Faller = person with 2 or more falls.</p>
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Hoang et al, 2016 Prospective cohort	<p><i>Inclusion Criteria</i></p> <ol style="list-style-type: none"> 1. Diagnosed with Multiple Sclerosis using standardised criteria. 2. Over age 18 (Other varying criteria for the different sites- US, UK and Australian study sites all had slightly different criteria). <p><i>Exclusion Criteria</i></p> <ol style="list-style-type: none"> 1. Inability to give informed consent or unable to follow instructions for study participation. 	<p>416 people with Multiple Sclerosis: Mean age 51.5 (range from 21-84), Male: Female = 111: 305, Mean disease duration = 13.7 years (9.9), Mean Expanded Disability Status scale = 4.03 (range 0-6.5), 62% had relapse remitting, Faller: Non-faller = 225: 191 352 controls: Male: Female = 78:274, Mean age 52.8 (range 21-84).</p>	<p>Physiological Profile Assessment, Prospective falls diaries for 3 months.</p>	<p>Different fall definitions were used for different test sites. For the Australian site a fall was defined as “unintentionally coming to the ground or other lower level and other than a consequence of sustaining a violent blow, loss of consciousness, sudden onset of paralysis as in stroke or epileptic or seizure”. For the UK and US sites a fall was defined as “a slip or trip in which participants came to rest on the ground or floor or lower level”</p> <p>Non frequent faller = 0 or 1 fall, frequent faller = 2 or more falls.</p>
Kasser et al, 2014 Prospective cohort	<p><i>Inclusion Criteria</i></p> <ol style="list-style-type: none"> 1. No relapse in prior 3 months. 2. Independent activities of daily living and driving. 3. Sufficient cognitive function to complete all questionnaires. 	<p>99 people with Multiple Sclerosis: All female, Mean age of 50.5 (8.38), Expanded Disability Status scale mean 2.97 (1.3), Faller: Non-faller = 35:22 (full data for N=67)</p>	<p>Prospective falls recording for a 12-month period. The Survey of Activities and Fear of Falling in the Elderly.</p>	<p>Fall defined as any unexpected loss of balance that resulted in whole body contact with the ground.</p> <p>Faller = person with 1 or more falls.</p>
Nilsagard et al, 2009	<p><i>Inclusion Criteria</i></p> <ol style="list-style-type: none"> 1. Expanded Disability Status scale score between 3.5 and 6. 	<p>76 People with Multiple Sclerosis:</p>	<p>Prospective falls recall (over 3 month period) and also</p>	<p>Fall definition not stated.</p>

Prospective cohort	<p>2. Age 18-75.</p> <p><i>Exclusion criteria</i></p> <ol style="list-style-type: none"> 1. Difficulty in understanding questions or filling in the questionnaires. 2. Evident hearing or visual deficit. 	<p>Mean age of fallers 50 (range 25-71) and of non-fallers 50 (range 32-75), Male: Female=6:22 in the non-fallers group and 13:35 in the fallers group, Median Expanded Disability Status scale of non-fallers 4.0 (range 3.0-6.0) and of fallers 5.0 (range 3.5-6.0), Walking aid use, N=14 in the non-fallers group and N=36 in the fallers group. Faller: Non-faller = 48: 28</p>	<p>retrospective at end of the 3 months.</p> <p>Berg balance scale, Four Square Step test, Timed Up and Go Cognitive.</p>	<p>Faller = person with 1 or more falls</p>
<p>Prosperini et al, 2013</p> <p>Prospective cohort</p>	<p><i>Inclusion Criteria:</i></p> <ol style="list-style-type: none"> 1. Age from 18 to 55. 2. Expanded Disability Status scale score of 0 to 5.5. 3. Clinical stability for at least 6 months. <p><i>Exclusion Criteria:</i></p> <ol style="list-style-type: none"> 1. Pregnancy. 2. Severely blurred vision. 3. Change in medication in the previous 3 months. 4. Concomitant otological or vestibular disease (not related to Multiple Sclerosis). 	<p>100 People with Multiple Sclerosis:</p> <p>Mean age 38.2 (9.6), Male: Female =36:64, Median Expanded Disability Status scale 3.2 (1.0-5.0), Mean disease duration 9.5 (6.4)</p> <p>Faller: Non-faller = 41: 59</p>	<p>Prospective falls recall (over 3 months).</p> <p>Berg balance scale.</p>	<p>Fall defined as an unexpected contact of any part of the body with the ground.</p> <p>Faller = person with 1 or more falls</p>

	<p>5. Cardiovascular and respiratory disorders.</p> <p>6. Psychiatric disorders.</p> <p>7. Severe cognitive impairment.</p>				
Tajali et al, 2017 Prospective cohort	<p><i>Inclusion Criteria:</i></p> <ol style="list-style-type: none"> 1. A definite diagnosis of MS as diagnosed by a neurologist. 2. Expanded Disability Status scale score of 0 to 5.5. 3. No clinical relapse in 30 days prior to testing. <p><i>Exclusion Criteria:</i></p> <ol style="list-style-type: none"> 1. Self-report of other conditions known to affect balance and gait. 2. Uncorrected visual impairment. 3. Severe cognitive impairment. 	<p>84 People with Multiple Sclerosis:</p> <p>Mean age of fallers = 30.29 (8.87) and of non-fallers = 33.8 (7.83)</p> <p>Male: Female = 7:36 in non-fallers and 15:26 in fallers,</p> <p>Mean Expanded Disability Status scale = 3.03 (1.29) for non-fallers and 4.14 (1.00) for fallers,</p> <p>Mean disease duration 4.02 (4.15) for non-fallers and 5.48 (5.19) for fallers,</p> <p>Faller: Non-faller = 41: 43</p>	<p>Prospective falls recall over 6 months.</p> <p>Timed Up and Go test, Activities, Balance and Confidence scale, Falls Efficacy Scale International.</p>	<p>Fall defined as any unexpected event that results in ending up on the ground, floor, or any lower surface.</p> <p>Faller = person with 1 or more falls</p>	
Vister et al, 2017 Prospective cohort	<p><i>Inclusion Criteria</i></p> <ol style="list-style-type: none"> 1. Diagnosed with Multiple Sclerosis using standardised criteria. 2. Over age 18 3. Able to walk 10 metres with or without a mobility aid. 4. Able to stand unsupported for thirty seconds. 	<p>210 People with Multiple Sclerosis:</p> <p>Mean age 50.8 (11.1),</p> <p>Male: Female = 58:152,</p> <p>Mean disease duration 9.9 (7.0),</p> <p>58% had relapse remitting Multiple Sclerosis,</p>	<p>Prospective falls recall (over 6 months).</p> <p>Physiological Profile Assessment, Falls Efficacy Scale International.</p>	<p>Fall defined as unintentionally coming to the ground or some lower level and other than as a consequence of sustaining a violent blow, loss of consciousness, sudden onset of paralysis as in stroke, or an epileptic seizure.</p> <p>Faller = person with 1 or more falls.</p>	

	<i>Exclusion Criteria</i> 1. Inability to give informed consent or unable to follow instructions for study participation secondary to impaired cognition or insufficient English.	49% using a mobility aid. Faller: Non-faller = 126: 84		
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Appendix 2.4: Descriptive characteristics of cross-sectional studies

Author, year Study Design	Eligibility Criteria	Recruited	Assessment Measures of Falls and Balance	Fall Definition and Classification
Cameron et al, 2014 Study design not reported.	Not reported	56 people with Multiple Sclerosis: Fallers: Non-fallers = 28: 26	Retrospective falls recall (over past 2 and 12 months), Mini-BESTest.	Fall definition not stated. Faller classification not stated.
Carling et al, 2016 Baseline data from a Randomised Controlled trial	<i>Inclusion Criteria:</i> 1. Multiple Sclerosis diagnosis according to McDonald criteria 2. Walking distance not exceeding 200m (with or without an aid) 3. Able to transfer from chair to plinth with minimal assistance (to be able to participate in the intervention). <i>Exclusion Criteria:</i> 1. Cognitive impairment limiting ability to participate in the study 2. Recent medical care in the past 3 months related to walking impairment 3. Balance rehab administered by a health	51 people with Multiple Sclerosis: Male: Female = 16:35 12% had relapse remitting, 63% had secondary progressive Multiple Sclerosis, Mean age 58 (10.24), Mean Expanded Disability Status score 6.11 (0.49) 86% used a walking aid, Disease duration = 20.85 years (12), 53% reported retrospective falls history. Fallers: Non-fallers = 28:24	Retrospective falls status reported at start of study (time period not stated), also prospective falls reporting but baseline data used based on retrospective faller/non-faller status. Berg balance scale. Timed Up and Go Falls Efficacy Scale International	Fall defined as an unexpected event in which participants come to rest on the ground, floor, or lower level. Faller classification not specified.

	professional in the past 30 days 4. On medication with 4-aminopyridine in the past 30 days.				
Cattaneo et al, 2002 Retrospective case-control.	<i>Inclusion Criteria:</i> 1. Able to walk independently or with a cane. 2. No cognitive or orthopaedic impairments.	50 people with Multiple Sclerosis: Mean age of fallers 40 (11.1), mean age of non-fallers 43.5 (11.6), Male: Female=38:62 in the fallers, 53:47 in non-fallers, Mean disease duration 13.4 (12.7) in fallers, 15.6 (12.2) in non-fallers, 32% of non-fallers used a cane, 59% of fallers used a cane. Fallers: Non-fallers = 17:33	Retrospective falls recall (2-month period pre-assessment), Equiscale Test.	No fall definition stated. Faller = person with 2 or more falls.	
Cattaneo et al, 2006 Cross-sectional	<i>Inclusion Criteria:</i> 1. Ability to stand independently more than 3 seconds. 2. Ability to walk for 6 m even with an assistive device. <i>Exclusion Criteria:</i> 1. Cognitive impairment	51 people with Multiple Sclerosis: Mean age 45.3 (18.1), Male: Female= 16:35, Mean disease duration 15.6 (7.6), 15 participants used a walking aid. Fallers: Non-fallers = 20: 31	Retrospective falls recall (1-month pre-assessment), Berg balance scale, Timed Up and Go, Dynamic Gait Index, Dizziness Handicap Inventory, Activities-specific Balance Confidence Scale.	Fall defined as any event that led to an unexpected contact with a support surface. Faller classification not stated.	

Cattaneo et al, 2012 Cross-sectional	2. Visual problems or impairment of VIII cranial nerve. <i>Inclusion Criteria:</i> 1. Ability to stand independently upright for 30 seconds. 2. Ability to walk for 6 m even with an assistive device.	47 people with Multiple Sclerosis: Mean age 52.01 (12.01), Male: Female=20:27, Mean disease duration 17.0 (9.9) Expanded Disability Status Scale median 5 (range 2.5-7.5) Faller: Non-faller = 11: 26	Retrospective falls record (2 months prior to assessment), Berg balance scale, Dynamic Gait Index.	Fall defined as an unexpected contact of any part of the body except for the feet with the ground. Faller = person with 1 or more falls.
Cattaneo et al, 2016 Baseline data from a randomised controlled trial.	<i>Inclusion Criteria:</i> 1. Ability to stand independently upright for 30 seconds with eyes open. 2. Ability to walk for 6 m even with an assistive device. <i>Exclusion Criteria:</i> 1. Ability to maintain single leg stance for 10 seconds. 2. Ability to maintain tandem stance for 30 seconds.	119 people with Multiple Sclerosis: Mean age 48.9 (11.1) in the intervention group, 46.7 (11.4) in the control, Male: Female=36:83, Mean disease duration 14 (8.6) in the intervention group, 12.9 (10.4) in the control, Faller: Non-faller =28: 91	Retrospective falls recall (over previous 2 months), Berg balance scale, Dynamic Gait Index, Timed Up and Go, Activities-specific Balance Confidence Scale.	Fall defined as an episode of unintentionally coming to rest on the ground or lower surface that was not the result of dizziness, fainting, sustaining a violent blow, loss of consciousness or other overwhelming external factor. Faller = person with 1 or more falls. Frequent faller = person with 2 or more falls.

Coote et al, 2013 Baseline and post treatment data from a randomised controlled trial.	3. Cognitive impairment that would limit participation in the assessment/intervention. No details given. These data were part of the baseline assessments of 1 arm of an exercise trial, the methods of which had been published previously.	111 people with Multiple Sclerosis; Mean age of fallers 55.6 (10.4), mean age of non-fallers 54.7 (11.1), Male: Female=17:38 in the fallers group, 23:32 in the non-fallers, Mean disease duration 16.6 (5) in the fallers, 14.1 (3) in non-fallers. Faller: Non-faller = 56: 55	Retrospective falls recall (over past 3 months), Berg balance scale.	Fall defined as an unexpected contact of any part of the body with the ground. Faller = person with 1 or more falls.	
Ganesan et al, 2015 Cross-sectional	<i>Inclusion Criteria:</i> 1. Expanded Disability Status Scale score of 4. 2. Able to stand and walk without any aid or orthosis at least 500 meters, 3. No relapse within the last three months, 4. Normal or corrected to normal vision <i>Subjects without Multiple Sclerosis</i>	18 people with Multiple Sclerosis: Mean age 52.7 (12.2) Male: Female=4:14, Mean disease duration 18.8 (9.4) Faller: Non-faller = 8: 10	Retrospective falls recall (over previous 12 months), Berg balance scale, Activities-specific Balance Confidence Scale.	No fall definition stated. Faller = person with 2 or more falls.	

Forsberg et al, 2013 Multi-centre cross sectional.	1. Age and gender matched to MS participants.			
	<p><i>Inclusion Criteria:</i></p> <ol style="list-style-type: none"> 1. Subjectively and objectively experience balance and walking limitations. 2. Ability to walk 100 m with an assistive device (similar to Expanded Disability Status Scale score of 1.0 to 6.0). <p><i>Exclusion criteria</i></p> <ol style="list-style-type: none"> 1. Cognitive dysfunction. 2. Difficulty understanding Swedish that affected the completion of self-reported scales. 	<p>81 people with Multiple Sclerosis: Mean age 49 (11) Male: Female=19:62, Mean disease duration 12.0 (8) Relapse remitting form = 53, Primary progressive form= 4, Secondary progressive = 24 Walking aid indoors, N= 12, Walking aid outdoors, N= 38 Faller: Non-faller = 30: 51</p>	Retrospective falls recall (over previous 2 months), Dynamic Gait Index, Timed Up and Go, Four square step test.	<p>Fall defined as an unexpected contact of any part of the body with the ground.</p> <p>Faller = person with 1 or more falls.</p>

<p>Forsberg et al, 2016</p> <p>Baseline data from a multi-centre randomised controlled trial.</p>	<p><i>Inclusion Criteria:</i></p> <ol style="list-style-type: none"> 1. Definite Multiple Sclerosis diagnosis. 2. Able to walk 100 m (with or without an aid). 3. Able to get up from the floor with minimal assistance. 4. Unable to maintain tandem stance position for 30 seconds. <p><i>Exclusion criteria</i></p> <ol style="list-style-type: none"> 1. Cognitive dysfunction. 2. Difficulty understanding Swedish that affected the completion of self-reported scales. 	<p>73 people with Multiple Sclerosis:</p> <p>Mean age of intervention group 52 (10) and of control group 56.3 (11).</p> <p>Male: Female=7:28 in the intervention group, 7:31 in the control group,</p> <p>Mean disease duration 15 (9) in the intervention group and 16 (11) in the control,</p> <p>45% of the group had relapse remitting,</p> <p>Walking aid indoors, N= 12,</p> <p>Walking aid outdoors, N= 44</p> <p>Faller: Non-faller = 38:49</p>	<p>Retrospective falls recall (over previous 3 months),</p> <p>Berg balance scale,</p> <p>Four Square Step test,</p> <p>Timed Up and Go and Timed Up and Go cognitive,</p> <p>Functional gait Assessment,</p> <p>Activities-specific Balance Confidence Scale.</p>	<p>Fall defined as an unexpected event in which the participant comes to rest on the ground, floor, or lower level.</p> <p>Faller classification not stated.</p>
<p>Jacobs et al, 2012</p> <p>Cross-sectional</p>	<p><i>Inclusion Criteria:</i></p> <p><i>Subjects with Multiple Sclerosis</i></p> <ol style="list-style-type: none"> 1. Expanded Disability Status Scale score < 6. 2. No uncorrected hearing or visual deficit. <p><i>Subjects without Multiple Sclerosis</i></p> <ol style="list-style-type: none"> 1. No self-reported neurological, 	<p>13 people with Multiple Sclerosis:</p> <p>Mean age 50 (95% CI 43-56),</p> <p>Male: Female= 5:8,</p> <p>Mean disease duration 9.5 (95%CI 6.75-12.25),</p> <p>Expanded Disability Status Scale Median 2.5 (range 0-4.5).</p> <p>Faller: Non-faller = 7: 6</p>	<p>Retrospective falls recall (over previous 3 months),</p> <p>Balance Evaluations System Test.</p>	<p>No definition of fall stated.</p> <p>Faller = person with 1 or more falls.</p>

	<p>musculoskeletal or psychiatric disorders.</p> <p>2. No uncorrected hearing or visual deficit.</p> <p>3. Age and gender matched to the subjects with Multiple Sclerosis.</p>				
<p>Kalron et al, 2013</p> <p>Cross-sectional</p>	<p><i>Inclusion Criteria:</i></p> <ol style="list-style-type: none"> 1. Ability to walk without a mobility aid. 2. A neurologist confirmed diagnosis of relapse remitting Multiple Sclerosis. 3. Relapse free for at least 30 days prior to testing. <p><i>Exclusion Criteria:</i></p> <ol style="list-style-type: none"> 1. Orthopaedic disorders affecting mobility 2. Major depression or cognitive decline. 3. Pregnancy. 4. Blurred vision. 5. Cardiovascular disorders. 	<p>107 people with Multiple Sclerosis:</p> <p>Mean age of fallers 45.3 (12.4), mean age of non-fallers 39.6 (10.8),</p> <p>Male: Female= 26:34 in the fallers group and 19:28 in the non-fallers,</p> <p>Mean disease duration in fallers 7.7 (7.7) and in non-fallers 4.3 (6.5),</p> <p>Mean Expanded Disability Status scale in fallers 3.6 (1.5) and in non-fallers 1.7 (1.5).</p> <p>Faller: Non-faller = 52: 49</p>	<p>Retrospective falls recall (previous 6 months),</p> <p>Falls Efficacy Scale International.</p>	<p>No fall definition stated.</p> <p>Faller = person with 1 or more falls.</p>	
<p>Kalron et al, 2014</p> <p>Cross sectional</p>	<p><i>Inclusion Criteria:</i></p> <ol style="list-style-type: none"> 1. Neurologist confirmed diagnosis of relapse 	<p>101 people with Multiple Sclerosis:</p> <p>Mean age 40.2 (11.9),</p> <p>Male: Female=41:60,</p>	<p>Retrospective recall of falls (over 1 year),</p> <p>Falls Efficacy Scale International.</p>	<p>Fall defined as an event when the participant unintentionally came to rest</p>	

	<p>remitting Multiple Sclerosis.</p> <p>2. People with Multiple Sclerosis who had undergone computerised neuropsychological testing (as data retrospectively evaluated from a computerised database).</p> <p>3. People with Multiple Sclerosis who had filled out the self-report forms Multiple Sclerosis Walking Scale-12, Falls Efficacy Scale International, and falling status questionnaires.</p> <p>4. People with Multiple Sclerosis who had a lab-based gait assessment using the GAITRite electronic mat.</p> <p>5. All cognitive, gait and self-reported forms completed within a 14-day range.</p> <p><i>Exclusion Criteria:</i></p> <p>1. Pregnancy</p>	<p>Mean disease duration 5.4 (6.3), Mean Expanded Disability Status scale 3.0 (1.8) (range 1.5-6).</p> <p>Faller: Non-faller = 60: 47</p>		<p>on the ground or a lower level.</p> <p>Faller = person with 1 or more falls.</p>
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	<p>2. Subjects with orthopaedic disorders that could affect mobility.</p> <p>3. Blurred vision.</p> <p>4. Cardiovascular disorders.</p> <p>5. On steroids or fampridine.</p> <p>6. No history of psychiatric problems.</p>				
<p>Kalron et al, 2016 (Ground Reaction Forces)</p> <p>Cross sectional</p>	<p><i>Inclusion Criteria:</i></p> <ol style="list-style-type: none"> 1. Definite diagnosis of Multiple Sclerosis. 2. Expanded Disability Status Scale of less than 7. 3. Able to walk at least 20 m without a rest. 4. Relapse free for the previous 30 days. <p><i>Exclusion Criteria:</i></p> <ol style="list-style-type: none"> 1. Orthopaedic disorders affecting mobility. 2. Pregnancy. 3. Blurred vision. 4. Cardiovascular or respiratory conditions. 5. On steroids or fampridine. 	<p>402 people with Multiple Sclerosis:</p> <p>Male: Female = 153:249,</p> <p>Mean age 42.1 (14.1),</p> <p>Mean Expanded Disability Status Scale 2.7 (1.7),</p> <p>Mean disease duration = 6 years (7.4),</p> <p>97% had relapse remitting form.</p> <p>Faller: Non-faller = 165:192</p>	<p>Retrospective falls recall (over the previous year),</p> <p>Timed Up and Go,</p> <p>Four Square Step test,</p> <p>Falls Efficacy Scale International.</p>	<p>No fall definition stated.</p> <p>Faller = person with 2 or more falls.</p>	

<p>Kalron et al, 2016 (Validity of Four-Square Step Test) Cross sectional</p>	<p><i>Inclusion Criteria:</i></p> <ol style="list-style-type: none"> 1. Definite diagnosis of Multiple Sclerosis. 2. Expanded Disability Status Scale of less than 6. 3. Relapse free for the previous 30 days, 4. Outcome measures assessed within a 3-month interval (data taken from a registry). <p><i>Exclusion Criteria:</i></p> <ol style="list-style-type: none"> 1. Orthopaedic disorders affecting mobility. 2. Pregnancy. 3. Blurred vision. 4. Cardiovascular or respiratory conditions. 5. On steroids or fampridine. 	<p>218 people with Multiple Sclerosis: Male: Female = 85:133, Mean age 43.2 (13.5), Mean Expanded Disability Status Scale 3.1 (1.3), Mean disease duration = 7.5years (7.7), Faller: Non-faller = 111:107, 95% had relapse remitting form.</p>	<p>Retrospective falls recall (over the previous year), Falls Efficacy Scale International, Timed Up and Go, Four Square Step test.</p>	<p>Fall defined as an event where the participant unintentionally came to rest on the ground or a lower level. Faller = person with 2 or more falls.</p>
<p>Kalron et al, 2016 (Walk Ratio) Cross sectional</p>	<p><i>Inclusion Criteria:</i></p> <ol style="list-style-type: none"> 1. Definite diagnosis of Multiple Sclerosis. 2. Expanded Disability Status Scale of less than 6. 3. Relapse free for the previous 30 days, 4. Outcome measures assessed within a 3-month 	<p>229 people with Multiple Sclerosis: Male: Female = 86:143, Mean age 43.4(12.4), Mean Expanded Disability Status Scale 1.7 (0.7), Mean disease duration = 6.2 years (7.1),</p>	<p>Retrospective falls recall (over the previous year), Falls Efficacy Scale International, Timed Up and Go.</p>	<p>Fall defined as an event where the participant unintentionally came to rest on the ground or a lower level. Faller = person with 2 or more falls.</p>

	<p>interval (data taken from a registry).</p> <p><i>Exclusion Criteria:</i></p> <ol style="list-style-type: none"> 1. Orthopaedic disorders affecting mobility. 2. Pregnancy. 3. Blurred vision. 4. Cardiovascular or respiratory conditions. 5. On steroids or fampridine. 	<p>Faller: Non-faller = 110:119, 94% had relapse remitting form.</p>		
<p>Kalron et al, 2017</p> <p>Cross-sectional</p>	<p><i>Inclusion Criteria:</i></p> <ol style="list-style-type: none"> 1. Definite diagnosis of Multiple Sclerosis. 2. Expanded Disability Status Scale of less than 7 or able to walk at least 20 metres without rest. 3. Relapse free for the previous 30 days, 4. Outcome measures assessed within a 3-month interval (data taken from a registry). <p><i>Exclusion Criteria:</i></p> <ol style="list-style-type: none"> 1. Orthopaedic disorders affecting mobility. 2. Pregnancy. 	<p>285 people with Multiple Sclerosis: Male: Female = 109:176, Mean age 44.5(13.4), Mean Expanded Disability Status Scale 3.5 (1.6), Mean disease duration = 8.1 years (8.1), Faller: Non-faller = 126:104, 92% had relapse remitting form.</p>	<p>Retrospective falls recall (over the previous year), Falls Efficacy Scale International, Timed Up and Go, Four Square Step test.</p>	<p>Fall was defined as an event where the participant came to rest unintentionally on the ground, floor or a lower level.</p> <p>Faller = person with 2 or more falls.</p>

<p>Ross et al, 2016</p> <p>Cross sectional cohort</p>	<p>2. Ongoing relapse affecting balance.</p> <p>3. Another disease preventing them from completing the measures.</p> <p><i>Inclusion Criteria:</i></p> <ol style="list-style-type: none"> 1. Primary diagnosis of Multiple Sclerosis. 2. Medically stable. 3. Independently mobile with or without an aid. 4. Over the age of 18. 	<p>52 people with Multiple Sclerosis:</p> <p>Mean age of total group 45.73 (5.65),</p> <p>Male: Female = 15:37,</p> <p>Mean disease duration 10.87 (8.48),</p> <p>Mobility aid use: 38% of the group,</p> <p>81% of the group had relapse remitting.</p> <p>Faller: Non-faller = 15: 37</p>	<p>Retrospective falls record over past 3 months, Mini-BESTest Berg balance scale.</p>	<p>Fall defined as an unexpected event in which the participants came to rest on the ground, floor, or lower level.</p> <p>Faller classification not stated.</p>
<p>Sosnoff et al, 2011</p> <p>Cross sectional</p>	<p><i>Inclusion Criteria:</i></p> <ol style="list-style-type: none"> 1. Ability to walk independently, with a mobility aid if needed. 2. Comprehension of written and spoken English. 3. Relapse free for 30 days. 	<p>52 people with Multiple Sclerosis:</p> <p>Mean age of fallers 56.3 (9.7) and of non-fallers 49.1 (12.1), Male: Female=8:44,</p> <p>Mean disease duration for fallers 16.9 (10.6) and for non-fallers 9.9 (6.3),</p> <p>Median Expanded Disability Status Scale for fallers 4.5 (IQR 2.5) and for non-fallers 3.0 (IQR 2.0),</p>	<p>Retrospective falls recall (over previous 12 months), Timed Up and Go, Six spot step test.</p>	<p>Fall defined as an event where the participant unintentionally came to rest on the ground or a lower level.</p> <p>Faller = person with 1 or more falls.</p>

Sung et al, 2016 Secondary data analysis of baseline data from a randomised controlled trial.	<p><i>Inclusion Criteria:</i></p> <ol style="list-style-type: none"> 1. Neurologist confirmed diagnosis of Multiple Sclerosis. 2. Ability to walk at least 25 feet, with a mobility aid if needed. 3. Comprehension of written and spoken English. 4. Over age 18. 	<p>Mobility aid use in the fallers group was 50% and in non-fallers was 13%. Faller: Non-faller = 29:23</p> <p>92 people with Multiple Sclerosis: Mean age 59.1 (7.3), Male: Female=23:69, Mean disease duration was 15.6 (8.5), Median Expanded Disability Status Scale for the group 6 (IQR 1.5), 54% had relapse remitting, Use of mobility aid N=64. Faller: Non-faller = 58:34</p>	<p>Retrospective falls recall (over previous 3 months), Berg balance scale.</p>	<p>Fall defined as an event where the participant unintentionally came to rest on the ground or a lower level.</p> <p>Faller classification not stated.</p>	
Van Vliet et al, 2015 Cross sectional	<p><i>Inclusion Criteria</i></p> <ol style="list-style-type: none"> 1. Over age 18. 2. Definite diagnosis of Multiple Sclerosis. 3. Multiple Sclerosis disease steps 0-5. 4. Able to stand unsupported for 30 seconds. 5. Able to walk 10 m with or without a mobility aid. <p><i>Exclusion Criteria</i></p>	<p>210 people with Multiple Sclerosis: Mean age of 51 (11.1) Male: Female = 62:148 Mean disease duration = 12.68 (9.08) 59.9% of group had relapse remitting, 47% used a mobility aid Faller: Non-faller = 159:51</p>	<p>Retrospective falls recall (over previous 12 months), Falls Efficacy Scale International.</p>	<p>Fall defined as unintentionally coming to the ground or some lower level and other than as a consequence of sustaining a violent blow, loss of consciousness, sudden onset of paralysis as in stroke or an epileptic seizure.</p> <p>Faller = person with 1 or more falls.</p>	

Ytterberg et al, 2013 Cross sectional	<p>1. Inability to understand instructions for the assessment due to poor English or impaired cognition.</p> <p><i>Inclusion Criteria</i></p> <ol style="list-style-type: none"> 1. Living and registered as a resident in Stockholm. 2. Clinical confirmation of Multiple Sclerosis diagnosis and informed of same. 3. No other severe psychiatric or neurological illness. 		<p>164 people with MS: Median age of fallers 52 (IQR 43-58) and of non-fallers 50 (IQR 42-60), Male: Female=20:42 in the fallers group and 24:76 in the non-fallers, Mild Expanded Disability Status Scale (1-3.5), N=10 in the fallers and 39 in the non-fallers, Moderate/severe Expanded Disability Status Scale (4-9.5), N=52 in the fallers and 63 in the non-fallers. Faller: Non-faller = 62: 102</p>		Retrospective falls recall (over the previous 3 months), Lindmark Motor Capacity Assessment.		<p>Fall defined as an individual coming to rest on the ground or at some other lower level.</p> <p>Faller = person with 1 or more falls.</p>
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Appendix 5.1: TRIPOD Checklist, Prediction model Development

Section/ Topic		Checklist Item	Page
Title and abstract			
Title	1	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	108
Abstract	2	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	110
Introduction			
Background and objectives	3a	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	111,112
	3b	Specify the objectives, including whether the study describes the development or validation of the model or both.	113
Methods			
Source of data	4a	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	113,114
	4b	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	113
Participants	5a	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	113
	5b	Describe eligibility criteria for participants.	113
	5c	Give details of treatments received, if relevant.	NA
Outcome	6a	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	114
	6b	Report any actions to blind assessment of the outcome to be predicted.	NA
Predictors	7a	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	115
	7b	Report any actions to blind assessment of predictors for the outcome and other predictors.	NA
Sample size	8	Explain how the study size was arrived at.	116
Missing data	9	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	116
Statistical analysis methods	10a	Describe how predictors were handled in the analyses.	117
	10b	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	117
	10d	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	117
Risk groups	11	Provide details on how risk groups were created, if done.	NA
Results			
Participants	13a	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	118

	13b	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	Table 5.1, pg 119
Model development	14a	Specify the number of participants and outcome events in each analysis.	120, 121
	14b	If done, report the unadjusted association between each candidate predictor and outcome.	Appendix 5.3
Model specification	15a	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	122 Table 5.3
	15b	Explain how to use the prediction model.	127
Model performance	16	Report performance measures (with CIs) for the prediction model.	121,122
Discussion			
Limitations	18	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	126
Interpretation	19b	Give an overall interpretation of the results, considering objectives, limitations, and results from similar studies, and other relevant evidence.	124, 125
Implications	20	Discuss the potential clinical use of the model and implications for future research.	128
Other information			
Supplementary information	21	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	NA
Funding	22	Give the source of funding and the role of the funders for the present study.	Title page

Appendix 5.2: Falls Screening Questionnaire

Please answer yes or no to the following questions:

Gender, male	
Do you have concerns or worries about falling?	
Do you use a cane or a walker at any time?	
Do you use more than one mobility aid over the course of a typical week?	
Is your MS course stable?	
Do you have problems with your balance?	
Do you have problems with your bladder or bowel?	
Do you have problems with poor concentration or forgetfulness?	
Have you had a fall in the last three months?	
Do you have stiffness or spasms in your limbs?	
Have you been told you have osteoporosis?	
Do you have fatigue that interferes with everyday tasks?	
Do you have reduced strength in your legs?	
Do you have problems with reduced or abnormal sensations?	
Do you have problems doing fiddly things with your hands?	
Do you have problems doing two things at once?	

Appendix 5.3 Data Collection Tool for Prospective Cohort Study

St. Vincent's Health**care**
GROUP LIMITED



UNIVERSITY of LIMERICK
OLLSCOIL LUIMNIGH

**“Development of a Falls Risk Prediction Tool for
Use with People with Multiple Sclerosis”**

Clinical Report Form

Patient Demographic Information

1. Participant Code: _____SVFP_____
2. Date of Birth: _____
3. Gender:

Male	<input type="checkbox"/>
Female	<input type="checkbox"/>
4. EDSS: _____
5. Length of time since diagnosis (Months):_____
6. Length of time since symptoms first experienced (Months):_____
7. Type of Multiple Sclerosis:

Primary Progressive	<input type="checkbox"/>
Secondary Progressive	<input type="checkbox"/>
Relapsing Remitting	<input type="checkbox"/>
Benign	<input type="checkbox"/>
Unknown	<input type="checkbox"/>
8. Over the last year the participant's MS has been:

Stable	<input type="checkbox"/>
Improving	<input type="checkbox"/>
Deteriorating	<input type="checkbox"/>
Variable	<input type="checkbox"/>
9. In general, would you consider your health to be:

Excellent	<input type="checkbox"/>
Good	<input type="checkbox"/>
Fair	<input type="checkbox"/>
Poor	<input type="checkbox"/>
Unsure	<input type="checkbox"/>
10. Do you ever use a walking aid:

Yes	<input type="checkbox"/>
No	<input type="checkbox"/>

****If participant answered "No" to question 10, progress straight to question 14****

11. Type of walking aid(s) used:
- | | |
|------------------------|--------------------------------|
| One walking stick | <input type="checkbox"/> |
| Two walking sticks | <input type="checkbox"/> |
| Tripod | <input type="checkbox"/> |
| Zimmer Frame | <input type="checkbox"/> |
| Three wheeled walker | <input type="checkbox"/> |
| Four wheeled walker | <input type="checkbox"/> |
| One elbow crutch | <input type="checkbox"/> |
| Two elbow crutches | <input type="checkbox"/> |
| Scooter | <input type="checkbox"/> |
| Wheelchair | <input type="checkbox"/> |
| Other (Please specify) | <input type="checkbox"/> _____ |
12. When do you use your aid(s):
- | | |
|-------------------------|--------------------------------|
| At all times | <input type="checkbox"/> |
| Only indoors | <input type="checkbox"/> |
| Only outdoors | <input type="checkbox"/> |
| Only on uneven surfaces | <input type="checkbox"/> |
| Other (Please specify) | <input type="checkbox"/> _____ |
13. Length of time since participant began using their primary aid (Months):
- _____
14. Current employment status:
- | | |
|--------------------------|--------------------------|
| Full Time | <input type="checkbox"/> |
| Part Time | <input type="checkbox"/> |
| Student | <input type="checkbox"/> |
| Homemaker | <input type="checkbox"/> |
| Unemployed | <input type="checkbox"/> |
| Retired | <input type="checkbox"/> |
| Unable to work due to MS | <input type="checkbox"/> |
15. Are you currently taking any prescribed medication:
- | | |
|-----|--------------------------|
| Yes | <input type="checkbox"/> |
| No | <input type="checkbox"/> |

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	100
---	---	---	---	---	---	---	---	---	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	-----

Falls screening questionnaire

Please answer yes or no to the following questions:

Gender	
Do you have concerns or worries about falling?	
Do you use a cane or a walker at any time?	
Do you use more than one mobility aid over the course of a typical week?	
Is your MS course stable?	
Do you have problems with your balance?	
Do you have problems with your bladder or bowel?	
Do you have problems with poor concentration or forgetfulness?	
Have you had a fall in the last three months?	
Do you have stiffness or spasms in your limbs?	
Have you been told you have osteoporosis?	
Do you have fatigue that interferes with everyday tasks?	
Do you have reduced strength in your legs?	
Do you have problems with reduced or abnormal sensations?	
Do you have problems doing fiddly things with your hands?	
Do you have problems doing two things at once?	

Symbol Digit Modalities Test

KEY

(÷	┌	┐	└	>	+)	÷
1	2	3	4	5	6	7	8	9

[illegible][illegible][illegible][illegible][illegible][illegible][illegible]

+ 	- 	(> 	[- 	(> 	- 	+ 	= 	+) 	-
-------	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------

Scoring Sheet

Participant Code: _____SVFP_____

SDMT

Trial (90 sec)	Score
1	

TUG

Walking Aid used _____

Trial	Time(seconds)
Practice	
1	
2	
3	

TUG-Cognitive

Walking Aid used: _____

Trial	Time(seconds)
Practice	
1	
2	
3	

Cognitive Strategies

No change in gait, correct numbers	Gait similar, number errors	Errors in numbers and gait but carry on regardless	Stop think step	Synchronise step and think	Gait wrong, numbers correct

Appendix 5.4: Variables for Inclusion in Model; 20 Potential Predictor

Variables with a p value ≤ 0.2 after Bivariate Analysis

Variable	No falls (n=44)	One or more falls (n=56)	P-value
DEMOGRAPHIC INFORMATION:			
Gender	12 M (27.2%) 32 F (72.7%)	22 M (39.3%) 34 F (60.7%)	0.21
MS course past year	Stable or improving 18 (41%) Deteriorating 19 (43%) Variable 7 (16%)	Stable or improving 14 (25%) Deteriorating 35 (63%) Variable 7 (13%)	0.15
Fall in past 3 months (yes)	15 (34.1%)	35 (62.5%)	0.01
MOBILITY STATUS:			
Uses a walking aid (yes)	29 (65.9%)	44 (78.6%)	0.16
MEDICATIONS:			
Currently taking prescribed meds (yes)	43 (97.7%)	51 (91.1%)	0.16
Taking Category G/Genitourinary and Sex Hormones (yes)	5 (11.4%)	18 (32.1%)	0.01
Taking Category J/anti-infectives (yes)	1 (2.3%)	6 (10.7%)	0.10
MS SYMPTOM INTERFERENCE:			
Problems with balance or mobility	Interferes a little 24 (54.5%) Interferes a great deal 20 (45.5%)	Interferes a little 20 (35.7%) Interferes a great deal 36 (64.3%)	0.06
Depression	Not a problem 30 (68.2%) Interferes a little or interferes a great deal 14 (31.8%)	Not a problem 30 (53.6%) Interferes a little or interferes a great deal 26 (46.4%)	0.14
Problems seeing	Not a problem 29 (65.9%) Interferes a little or interferes a great deal 15 (34.1%)	Not a problem 45 (80.4%) Interferes a little or interferes a great deal 11 (19.6%)	0.10
Problems with bladder control	Not a problem 16 (36.4%) Interferes a little 14 (31.8%) Interferes a great deal 14 (31.8%)	Not a problem 10 (17.9%) Interferes a little 26 (46.4%) Interferes a great deal 20 (35.7%)	0.10

FALLS SCREENING QUESTIONNAIRE (Yes/No ANSWERS):			
Uses a cane/walker (yes)	28 (63.6%)	44 (78.6%)	0.10
Is MS course stable (yes)	20 (45.5%)	16 (28.6%)	0.08
Problems with bladder/bowel (yes)	32 (72.7%)	50 (89.3%)	0.03
Fall in past 3 months (yes)	15 (34.1%)	34 (60.7%)	0.01
Stiffness/spasms in limbs (yes)	33 (75%)	48 (85.7%)	0.18
Problems dual tasking (yes)	16 (36.4%)	31 (55.4%)	0.06
STRATEGIES WHEN DUAL TASKING:	*12 missing (not done for 1 st 12 participants)		
No change in gait, correct numbers	9 (25%)	7 (13.5%)	0.17
Gait wrong, numbers correct	5 (13.9%)	16 (30.8%)	0.07
OBJECTIVE MEASURES:			
TUG	Median 11.19 (8.56, 13.71)	Median 11.99 (9.53, 17.21)	0.09

Appendix 6.1 Falls Diary

Throughout this month, please write the number of falls you have each day and the number of falls that cause any injury. Please consider a fall as “an unexpected event in which you come to rest on the ground, floor, or lower level”. If you don’t have a fall put in 0 rather than leaving the box blank.

May 2015

	MON	TUE	WED	THUR	FRI	SAT	SUN
					1	2	3
Number of falls							
Number of falls causing injury							
	4	5	6	7	8	9	10
Number of falls							
Number of falls causing injury							
	11	12	13	14	15	16	17
Number of falls							
Number of falls causing injury							
	18	19	20	21	22	23	24
Number of falls							
Number of falls causing injury							
	25	26	27	28	29	30	31
Number of falls							
Number of falls causing injury							
Number of falls							
Number of falls causing injury							

Please write down the number of each type of injury as a result of any fall this month

☐ No injuries this month

	Head	Body	Arms	Legs
Bruises				
Cuts/scrapes				
Sprain/Strain				
Dislocation				
Broken Bone				

Please mark on the body where any fractures or broken bones occurred



Did you use any of the following medical or other services because of any falls this month?

☐ YES

☐ NO

Medical Service or Other Care	Number of times
Nurse visit	
Primary Care provider	
Specialist doctor visit (hospital or privately) What type of specialist?	
Emergency Department	
Admission to hospital How many days were you hospitalised?	
Other (please state)	

If you fell, for the first 2 falls, please answer the following questions

	Fall 1	Fall 2
What time of day did you fall?	Morning <input type="checkbox"/> Afternoon <input type="checkbox"/> Evening <input type="checkbox"/> Night <input type="checkbox"/>	Morning <input type="checkbox"/> Afternoon <input type="checkbox"/> Evening <input type="checkbox"/> Night <input type="checkbox"/>
Where did you fall?		
	Inside at home <input type="checkbox"/> Outside at home <input type="checkbox"/> Away from home <input type="checkbox"/>	Inside at home <input type="checkbox"/> Outside at home <input type="checkbox"/> Away from home <input type="checkbox"/>

Did you have a MS relapses this month?

☐ NO ☐

☐ YES → If yes please provide information on;

When did the relapse start? _____

How long did it continue? _____

What symptoms did you notice? _____

Did you visit a healthcare professional? _____

What treatment did you have? _____

What do you think caused you to fall? (Check more than one if necessary)

	Fall 1	Fall 2
Poor balance		
Weak legs or legs gave way		
Not using walking aid at all or using it incorrectly or using wrong walking aid		
Tripped/Slipped		
Transfer from surface to surface went wrong		
Not paying attention or being distracted		
Miscalculated a distance, under or overreaching		
Another medical problem unrelated to my MS		
Doing something risky		
Weather - Ice, rain, snow or wind		
Poor vision (didn't see an obstacle)		
Felt dizzy/faint		
Overheated (too hot)		
Fatigued		
I'm not sure		
Other (please give details)		

Did you lay on the ground or floor for more than 10 minutes because of any falls this month?

☐ YES ☐ NO

IF YES, please complete this chart

Time on the ground or floor	Number of times
Between 10 and 30 minutes	
Between 30 and 60 minutes	
For more than 60 minutes	

Did you need help to get up after any falls this month?

☐ YES ☐ NO

IF YES, please complete this chart

Type of help	Number of times
Help from a friend, family member or neighbour	
Help from the emergency service (e.g. Ambulance, Fire fighter)	